Hypertrophic cardiomyopathy: towards an optimal strategy

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Risk stratification in hypertrophic cardiomyopathy

3.1 Risk stratification for sudden cardiac death in hypertrophic cardiomyopathy: systematic review of clinical risk markers.

Christiaans I, van Engelen K, van Langen IM, Birnie E, Bonsel GJ, Elliott PM, Wilde AAM

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Abstract
We performed a systematic literature review of recommended ‘major’ and ‘possible’ clinical risk markers for sudden cardiac death (SCD) in hypertrophic cardiomyopathy (HCM). We searched Medline, Embase and Cochrane databases for articles published between 1971 and 2007. We included English language reports on HCM patients containing follow-up data on the endpoint (sudden) cardiac death using survival analysis. Analysis was undertaken using the quality of reporting of meta-analyses (QUORUM) statement checklist. The quality was checked using a quality assessment form from the Cochrane Collaboration. Thirty studies met inclusion criteria and passed quality assessment. The use of the six major risk factors (previous cardiac arrest or sustained ventricular tachycardia, non-sustained ventricular tachycardia, extreme left ventricular hypertrophy, unexplained syncope, abnormal blood pressure response, and family history of sudden death) in risk stratification for SCD as recommended by international guidelines was supported by literature. In addition, left ventricular outflow tract obstruction seems associated with a higher risk of SCD. Our systematic review provides sound evidence for the use of the six major risk factors for SCD in the risk stratification of HCM patients. Left ventricular outflow tract obstruction could be included in the overall risk profile of patients with a marked left ventricular outflow gradient under basal conditions.
Introduction
Hypertrophic cardiomyopathy (HCM) is a genetically heterogeneous heart muscle disorder characterised by myocardial hypertrophy in the absence of abnormal loading conditions. While it has been recognised for many decades that some patients with the disease die suddenly from ventricular arrhythmia, data from contemporary studies suggest that the overall risk is relatively small with annual sudden cardiac death (SCD) rates of 1% or less in most series. The challenge for clinicians is to identify the small cohort of patients who are at risk in order to target potentially lifesaving therapy with implantable cardioverter defibrillators (ICD).

In a joint consensus report of the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) dating from 2003, it is recommended that all patients with HCM should be assessed using an algorithm based on a small number of readily determined clinical parameters that are thought to reflect the severity of the underlying myocardial disease and therefore the risk of sudden cardiac death (Table 1). Based on the assumption that the number of risk factors corresponds to the magnitude of the risk of SCD, the report recommends consideration of an ICD in patients with one or more of the suggested clinical markers. While data from observational studies of patients with HCM that have received an ICD suggest that this approach to risk stratification identifies a cohort that benefits from therapy, a major limitation of the ACC/ESC guidelines is the lack of any systematic review of the relative predictive power of individual risk factors in different populations. In this study we set out to perform such a review, focusing on the validity of individual risk factors.

Methods

Literature search
Published studies on natural history, risk factors, and prognosis were identified by searching the electronic databases of Medline (1971 to December 2007), Embase (1980 to December 2007) and the Cochrane Library (all years). The search strategy was developed by the researchers and a clinical librarian. The search strategy was broad (high recall and low precision) and focused on the combination of three main search topics: HCM; death; and prognosis. A detailed search strategy was developed for use in Medline and then adapted for each database (Supplement 1). A manual follow-up search of key authors encountered most frequently in the field and of reference lists of included papers was performed.

Inclusion criteria
We included English language reports on a cohort of patients with HCM containing follow-up data on the endpoints cardiac (or cardiovascular) death or sudden death. Only articles analysing major or possible risk factors for SCD according to the ACC/ESC guidelines were included (Table 1). We required that possible correlations between the presence of a risk factor and the endpoint were investigated using a survival analysis (e.g. Cox regression) to limit heterogeneity between studies based on different methods of analysis. In many studies that used Cox regression analysis, the hazard ratio was presented as relative risk, risk ratio or odds ratio, although such terminology refers to relative probabilities at a fixed cumulative time interval, for example, after 2 years of follow-up. When referring to included studies, we left the risk term used in the study unaltered. In the figures, however, we used hazard ratios for the sake of uniformity.
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Data collection and analysis

Analysis was undertaken using the QUORUM (Quality Of Reporting Of Meta-analyses) statement checklist (Supplement 2). Meta-analysis of the data was performed (RevMan 4.3, Cochrane, Copenhagen, Denmark), but showed substantial heterogeneity ($I^2$ test) between the studies - the percentage of variance due to heterogeneity ranged from 34 to 95% for the major risk factors for SCD. Two reviewers (IC and KvE) independently checked the list of titles and abstracts identified by the search to determine whether an article contained relevant data. Selected articles and articles without abstract were read in full to confirm eligibility. All articles were subject to a quality assessment form for systematic reviews and meta-analyses from the Cochrane Collaboration. We extracted the following data from the selected articles: inclusion and exclusion criteria, patient characteristics (age, gender, presence of risk factors), study design (prospective or retrospective), follow-up duration, number of patients lost to follow-up, univariate and/or multivariate Cox regression analysis, type of endpoint (e.g. SCD and/or cardiovascular death), and hazard ratios.

An average value for the hazard ratio for SCD of each risk factor, extracted from the

### Table 1. Risk factors for sudden cardiac death in hypertrophic cardiomyopathy.

<table>
<thead>
<tr>
<th>Major Risk Factor</th>
<th>Possible in Individual Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior aborted cardiac arrest (ventricular fibrillation) or spontaneous sustained ventricular tachycardia</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Non-sustained ventricular tachycardia (Holter)</td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>Left ventricular outflow tract obstruction</td>
</tr>
<tr>
<td>Left ventricle thickness ≥30 mm</td>
<td>High-risk mutation</td>
</tr>
<tr>
<td>Abnormal exercise blood pressure</td>
<td>Intense (competitive) physical exertion</td>
</tr>
<tr>
<td>Family history of premature sudden cardiac death</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Search results.
Systematic review of risk factors for SCD

meta-analysis, is provided in the text. Some studies only report the significance level and not the hazard ratio. As these studies are not included in the meta-analysis and the included studies are heterogeneous, this average hazard ratio should be interpreted with caution. Average hazard ratios were not calculated for the possible risk factors because of the low number (≤ 2) of studies reporting the hazard ratio.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

Figure 1 summarises the search results. Our search identified 1376 unique articles. By reading the titles and abstracts, 1208 were excluded because they did not meet our inclusion criteria.
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Of the remaining 168, the full text version of the paper was obtained and evaluated. This excluded another 135 articles. Reasons for exclusion are listed in Figure 1. Of the 33 remaining articles, three did not pass quality assessment. Two of the three studies were excluded because they assessed only children. The third article included only HCM patients with symptoms of myocardial ischemia. Thus, the remaining 30 articles were subjected to data extraction (Figure 1, Tables 2 and 3). Several articles reported data collected from the same population of patients. Because these studies seemed to use different sub-samples, they were considered as separate studies.

Twelve of 30 studies reported on risk factors for SCD, 13 on risk factors for cardiovascular death (including SCD, heart transplantation, and death due to stroke or heart failure), and 5 reported on both endpoints.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-sustained ventricular tachycardia</td>
<td>≥ 3 consecutive ventricular beats at a rate of ≥ 120 beats per minute, lasting for &lt;30 seconds, evident on ambulatory (Holter) ECG recordings (^{17,19,29,35})</td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td>(1) loss of consciousness without a known causal factor or (2) ≥ 1 episode (^{12,24}) or ≥ 2 episodes (^{15,18}) of loss of consciousness without a known causal factor in the previous year</td>
</tr>
<tr>
<td>Extreme left ventricular hypertrophy</td>
<td>maximum left ventricular wall thickness ≥ 30 mm (^{31,32,34,36,38,39,40}) or ≥ 25 mm (^{18}) or ≥ 20 mm (^{44})</td>
</tr>
<tr>
<td>Abnormal exercise blood pressure</td>
<td>(A) Hypotensive response: decrease in systolic BP during the whole exercise period of &lt;25 mmHg (^{11,13,14}) or &lt;20 mmHg (^{38}) compared with the resting systolic BP or (B) Hypotensive response: (i) initial increase in systolic BP with a subsequent fall by peak exercise of &gt;15 mmHg (^{18}) or &gt;10 mmHg (^{13,15,16}) from baseline or the peak BP value or (b) decrease below baseline values in the absence of an initial rise (^{18}) or (c) sustained (&gt;1 minute) decrease in systolic BP of &gt;20 mmHg compared with baseline after an initial rise (^{18})</td>
</tr>
<tr>
<td>Family history of premature SCD</td>
<td>(1) SCD in a first degree relative (^{16,17}) or (2) SCD in ≥ 2 relatives &lt;40 years (^{12,13,15}) or (3) SCD in ≥ 2 first degree relatives &lt;40 years (^{33}) or (4) SCD in ≥ 1 relatives with HCM or ≥ 1 SCD &lt;50 years in a close relative without the diagnosis of HCM (^{30})</td>
</tr>
<tr>
<td>Left ventricular outflow tract obstruction</td>
<td>peak gradient ≥ 30 mmHg (^{4,9,25,26,31,34,35,37,38,39,40}) or ≥ 50 mmHg (^{4,9}) by Doppler echocardiography under basal (resting) conditions or provoked ≥ 50 mmHg (^{1,17})</td>
</tr>
</tbody>
</table>

Table 3. Definitions of risk factors for sudden cardiac death used in included studies.

### Major risk factors

**Prior aborted cardiac arrest and spontaneous sustained ventricular tachycardia**

Prospective data on survival of patients with HCM who survived a cardiac arrest are limited, and none of the included studies reported data on this risk factor. Studies only including HCM survivors of a cardiac arrest reported a significant association with future SCD, a 7-year mortality rate of ~33% or a 5-year SCD or ICD discharge rate of 41%.
Non-sustained ventricular tachycardia
Most included studies did not find a significant relation between non-sustained ventricular tachycardia (NSVT) and SCD. With increasing patient numbers in more recent studies, NSVT proved to be a significant independent risk factor for SCD, especially in the young. The average reported hazard ratio for NSVT was 2.89 (95% confidence intervals (CI): 2.21-3.58).

Unexplained syncope
Most studies did not demonstrate a statistically significant relation between unexplained syncope and either SCD or HCM-related death. Three studies reported a significant increase in SCD in patients with unexplained syncope. The average reported hazard ratio for unexplained syncope was 2.68 (95% CI: 0.97-4.38).

Extreme left ventricular hypertrophy
The number of studies reporting extreme left ventricular hypertrophy (LVH) as a significant risk factor for cardiac death or SCD approximates the number of studies that found no or a non-significant relationship between extreme LVH and cardiac death or SCD. The average reported hazard ratio for extreme LVH was 3.10 (95% CI: 1.81-4.40).

Abnormal blood pressure response to exercise testing
Some of the included studies found significantly more SCD in HCM patients with an abnormal blood pressure response (ABPR), but in one study the risk was only increased for patients aged 50 or younger. Other studies demonstrated only a non-significant increase in SCD or appropriate ICD discharge with ABPR, even in young patients. The average reported hazard ratio for ABPR was 1.30 (95% CI: 0.64-1.96).

Family history of SCD
Most included studies did not demonstrate a significant relationship between family history of SCD (FHSCD) and cardiac death or SCD. Three recent studies demonstrated that FHSCD was an independent but weak predictor for SCD. The average reported hazard ratio for FHSCD was 1.27 (95% CI: 1.16-1.38).

Combination of major risk factors
Several studies investigated the risk of SCD in the presence of combinations of major risk factors. The combination of a history of syncope with FHSCD was a significant predictor of SCD risk. Another study (using logistic regression) reported a significantly increased risk of a cardiac event (SCD, cardiac arrest or ICD discharge) in patients with a history of cardiac arrest, syncope and/or presyncope. The same combination of risk factors did not show to be a significant predictor for HCM-related death. Some studies investigated the number of risk factors in relation to the risk of SCD. One study found that two or more of the studied risk factors (ABPR, NSVT, extreme LVH, FHSCD, and syncope) in multivariate analysis provided a risk ratio of 5.6 (95% CI: 2.43-13.1, P = 0.002). Patients with two or more risk factors (12%) had an estimated annual SCD risk of 4-5%. In 2001, a relative risk of 2.00 (95% CI: 1.43-2.79, P = 0.0001) was reported per additional risk factor (one to three).
Figure 2. Hazard ratios for sudden cardiac death (filled square) or cardiovascular death (filled circle) for non-sustained ventricular tachycardia. The size of the squares and circles corresponds with the number of patients in the study. The bars represent the upper and lower 95% CI. Hazard ratios with CI >1 indicate a significant association with sudden cardiac death. When the hazard ratio is not specified in the article the significance level is provided; ‘s’ for a significant relationship and ‘ns’ for a non significant relationship are used. *, univariate analysis; †, hazard ratio for sudden cardiac death and appropriate implantable cardioverter defibrillator discharge; ‡, hazard ratio for sudden cardiac death and resuscitated cardiac arrest; §, hypertrophic cardiomyopathy patients ≤ 30 years.

Figure 3. Hazard ratios for sudden cardiac death (filled square) or cardiovascular death (filled circle) for unexplained syncope. Use of symbols as in Figure 2. ||, hypertrophic cardiomyopathy patients ≤ 50 years.

Figure 4. Hazard ratios for sudden cardiac death (filled square) or cardiovascular death (filled circle) for extreme left ventricular hypertrophy. Use of symbols as in Figure 2. ||, hypertrophic cardiomyopathy patients ≤ 50 years; #, extreme left ventricular hypertrophy defined as maximal wall thickness ≥ 25 mm.
Possible risk factors

**Atrial fibrillation**

Atrial fibrillation was associated with a higher risk of cardiovascular death in several studies. However, only one included study reported a significant correlation between atrial fibrillation and SCD (RR: 4.90, 95% CI: 1.49-16.67, P = 0.008). In contrast, three larger studies did not identify a significant relationship between atrial fibrillation and SCD.

**Myocardial ischaemia**

Three of the included studies assessed the prognostic impact of ischaemia using different clinical methodologies. A history of myocardial infarction proved to be a significant predictor for cardiac death, as well as microvascular dysfunction (HR: 0.14, 95% CI: 0.03-0.78, P = 0.02). In one study, severe coronary artery disease was a significant predictor for cardiac death (RR: 2.15, 95% CI: 1.27-3.70, P = 0.004) and SCD (RR: 2.77, 95% CI: 1.23-6.25, P = 0.01).

**Left ventricular outflow tract obstruction**

Several studies with large patient populations demonstrated a significant relationship between left ventricular outflow tract obstruction (LVOTO) and SCD or between LVOTO and HCM-related death. Smaller studies could not find such a relationship for SCD or cardiovascular death.

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**Figure 5.** Hazard ratios for sudden cardiac death (filled square) or cardiovascular death (filled circle) for abnormal blood pressure response. Use of symbols as in Figure 2. \[\text{\textdagger}\text{, hypertrophic cardiomyopathy patients \leq 50 years; \textdagger\textdagger, hypertrophic cardiomyopathy patients \leq 40 years.}\]

**Figure 6.** Hazard ratios for sudden cardiac death (filled square) or cardiovascular death (filled circle) for family history of sudden cardiac death. Use of symbols as in Figure 2. \[\text{\textdagger}, hypertrophic cardiomyopathy patients \leq 50 years.\]
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Genotype
None of the studies included in the search investigated genotype as separate risk factor. Since the discovery of the first HCM-related genes, many papers on genotype-phenotype correlations have been published. At first, specific mutations, mainly in the MYH7 gene, were described that were associated with a ‘malignant’ phenotype (decreased survival) or a ‘benign’ phenotype (normal longevity). Later studies have contradicted this suggested classification into ‘malignant’ and ‘benign’ mutations.

Mutations in the MYH7 gene were reported to cause a more severe phenotype with a younger age of onset, more LVH, and more sudden death than mutations in the MYBPC3 gene. However, all of these studies had the same limitations: small population size, low prevalence of each mutation, intra- and inter-familial variability in expression of the phenotype, and have been contradicted in more recent studies. Some genotype-phenotype correlations still hold. In families with a TNNT2 gene mutation, SCD can also occur at a younger age, even before ventricular hypertrophy is present. More recently, systematic genotyping revealed patients with two mutations in the same gene or in different genes, who have a more severe phenotype with a younger age of onset and more adverse events.

Physical exertion
None of the studies included evaluated this possible risk factor. Three studies reported on the circumstances preceding death. In two studies, about two-thirds of SCD occurred during exertion (32-44% during mild exertion and 22-32% during moderate to severe exertion).

Discussion
This is the first systematic analysis of the literature supporting current international guidelines on the assessment of sudden death risk in patients with HCM. The findings suggest that all recommended major risk factors are associated with an increased risk of sudden death, with the proviso that the power of some risk markers is substantially modified by age. The analysis provides few data to support the use of ‘possible’ risk factors, with the possible exception of LVOTO, which was associated with a higher risk of SCD in several large studies. Although LVOTO, unlike most other risk markers, is potentially modifiable with drug therapy, surgery, or alcohol septal ablation, there currently is only limited evidence that therapy for LVOTO has a beneficial effect on survival. Although we believe that the analysis does not support a move away from current practice guidelines that recommend invasive gradient reduction only in patients with severe drug refractory symptoms, our findings also suggest that LVOTO may be associated with an increased risk of SCD and could be included in the overall risk profile of patients with a marked left ventricular outflow gradient under basal conditions.

The approach to risk stratification recommended in the ACC/ESC consensus guidelines is based on the concept of global risk burden, whereby treatment decisions are determined by the presence of a small number of risk factors. The ACC/ESC guidelines for prevention of sudden death recommend ICD implantation in people with a history of sustained ventricular arrhythmia and in patients with one or more of the recommended risk factors. This review supports the notion that a prior cardiac arrest (ventricular fibrillation) or spontaneous VT as sole risk factor seems to be associated with a considerable increase in SCD risk, sufficient to advocate an ICD. Patients with only one of the other five major risk factors can also be at risk for SCD (or ventricular arrhythmias), but the wide CI suggest that the majority is probably
at low risk and the decision to implant an ICD for prophylactic reasons should be made on a case-by-case basis including the clinical presentation of the risk factor and other clinical parameters affecting prognosis and health status. There are data to show that patients with multiple risk factors are at greater risk, but these are mostly derived from one centre. However, all major risk factors have been shown to increase the risk of SCD independently and there is sufficient evidence to support the assumptions that patients with two or more risk factors have a higher risk of SCD than patients with only one risk factor.

**Limitations**

An accurate meta-analysis is prevented by the large heterogeneity between studies and the fact that many studies do not report their non-significant hazard ratios. Looking at our figures, and the average hazard ratios we can conclude that all major risk factors indeed are associated with an increased risk of SCD. The large CI due to the low event rate and small populations in many studies require cautious interpretation. Other factors biasing meta-analysis results are the possible overlap in patients between different studies from the same institutions and the use of univariate as well as multivariate hazard ratios in our estimation.

Prognostic studies on risk factors included in this systematic review all suffer from the same problems: (1) heterogeneity in the studied population, the studied risk factors, and the definition of risk factors (Table 3); (2) selection bias - data are almost exclusively from specialised centres with populations large enough to perform prognostic studies; (3) the modifying effect of therapy on risk factors is difficult to assess, for example, in LVOTO or ischaemia; (4) the large CI due to low event rates and small impact differences, making large patient cohorts and long follow-up necessary; and (5) studied risk factors are always clinically heterogeneous even when there is a strict definition, for example, incidental NSVT or recurrent NSVT.

Ideally, cardiologists would like to know the risk of SCD for their individual patient. It is a noble goal to be able to determine the risk of SCD at the individual level. Unfortunately, such a risk classification system is currently unavailable. As a first step, we need studies on group level to determine which risk factors appear to be associated with SCD. Our systematic review was designed to investigate the evidence for certain clinical markers being associated with a higher risk for SCD, but we are unable to develop a risk prediction model for the individual patient based on literature. We therefore stimulate further research on risk factors for SCD, especially on combinations and number of risk factors on the one hand and the risk of SCD on the other.

**Conclusion**

In this systematic review, we have validated the use of the six major risk factors in risk stratification for SCD as recommended in international guidelines, since they all seem to be associated with an increased risk of SCD. Left ventricular outflow tract obstruction is possibly associated with SCD and could be included in the overall risk profile of patients with a marked left ventricular outflow gradient under basal conditions. Further research into the risk associated with LVOTO and with the combined presence of >1 major risk factors is necessary.
References


Supplement 1. Search strategy.

Medline database
1 AND 2 AND 3

1) HCM
hypertrophic cardiomyopath* OR hypertrophic obstructive cardiomyopath* OR asymmetric septal hypertroph* OR idiopathic hypertrophic subaortic stenosis OR idiopathic hypertrophic subvalvular stenosis OR IHSS*

2) death
mortality OR death

3) prognosis

Embase database
1 AND 2 AND 3

1) HCM
hypertrophic cardiomyopathy or asymmetric septal hypertrophy or aorta subvalvular stenosis or idiopathic hypertrophic subaortic stenosis

2) death
death or mortality

3) prognosis
incidence or follow up studies or prognosis or prediction or disease course or risk or natural history

Cochrane library
Search 1 gave zero results.
1) HCM
hypertrophic cardiomyopathy or asymmetric septal hypertrophy or aorta subvalvular stenosis or idiopathic hypertrophic subaortic stenosis
## Supplement 2. QUORUM statement checklist

<table>
<thead>
<tr>
<th>Heading</th>
<th>Subheading</th>
<th>Descriptor</th>
<th>Reported? (Y/N)</th>
<th>Page number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td></td>
<td>Identify the report as a meta-analysis (or systematic review) of RCTs</td>
<td>Y</td>
<td>1</td>
</tr>
<tr>
<td><strong>Abstract</strong></td>
<td>Use a structured format</td>
<td></td>
<td>Y</td>
<td>2</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td><strong>Describe</strong></td>
<td>The clinical question explicitly</td>
<td>Y</td>
<td>2</td>
</tr>
<tr>
<td><strong>Data sources</strong></td>
<td>The databases (ie, list) and other information sources</td>
<td></td>
<td>Y</td>
<td>2</td>
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<tr>
<td><strong>Review methods</strong></td>
<td>The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics; and quantitative data synthesis in sufficient detail to permit replication</td>
<td>Y</td>
<td>2</td>
<td></td>
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<tr>
<td><strong>Results</strong></td>
<td>Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals) and subgroup analyses</td>
<td></td>
<td>Y</td>
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<tr>
<td><strong>Conclusion</strong></td>
<td>The main results</td>
<td></td>
<td>Y</td>
<td>2</td>
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<tr>
<td><strong>Introduction</strong></td>
<td><strong>Describe</strong></td>
<td>The explicit clinical problem, biological rationale for the intervention, and rationale for review</td>
<td>Y</td>
<td>3</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td><strong>Searching</strong></td>
<td>The information sources, in detail (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)</td>
<td>Y</td>
<td>4</td>
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<tr>
<td><strong>Selection</strong></td>
<td><strong>Inclusion and exclusion criteria</strong> (defining population, intervention, principal outcomes, and study design)</td>
<td></td>
<td>Y</td>
<td>4</td>
</tr>
<tr>
<td><strong>Validity assessment</strong></td>
<td>The criteria and process used (eg, masked conditions, quality assessment, and their findings)</td>
<td></td>
<td>Y</td>
<td>4, 5</td>
</tr>
<tr>
<td><strong>Data abstraction</strong></td>
<td>The process or processes used (eg, completed independently, in duplicate)</td>
<td></td>
<td>Y</td>
<td>4, 5</td>
</tr>
<tr>
<td><strong>Study characteristics</strong></td>
<td>The type of study design, participants' characteristics, details of intervention, outcome definitions, and how clinical heterogeneity was assessed</td>
<td></td>
<td>Y</td>
<td>4, 5</td>
</tr>
<tr>
<td><strong>Quantitative data synthesis</strong></td>
<td>The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data, how statistical heterogeneity was assessed; a rationale for any a priori sensitivity and subgroup analyses; and any assessment of publication bias</td>
<td>Y</td>
<td>4, 5</td>
<td></td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><strong>Trial flow</strong></td>
<td>Provide a meta-analysis profile summarising trial flow (see figure)</td>
<td>Y</td>
<td>Fig 1</td>
</tr>
<tr>
<td><strong>Study characteristics</strong></td>
<td>Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)</td>
<td></td>
<td>Y</td>
<td>Table 2, Table 3</td>
</tr>
<tr>
<td><strong>Quantitative data synthesis</strong></td>
<td>Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2x2 tables of counts, means and SDs, proportions)</td>
<td>Y</td>
<td>5-9, Fig 2-6</td>
<td></td>
</tr>
<tr>
<td><strong>Discussion</strong></td>
<td>Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest future research agendas</td>
<td>Y</td>
<td>9-11</td>
<td></td>
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</tbody>
</table>