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Myosin inhibitors for treatment of hypertrophic cardiomyopathy (Protocol)

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[Intervention Protocol]

Myosin inhibitors for treatment of hypertrophic cardiomyopathy

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

Primary objective

To assess the effects of myosin inhibitors compared to usual care or placebo on exercise capacity, need for septal reduction therapy, and all-cause mortality in people with hypertrophic cardiomyopathy (HCM).

Secondary objectives

To assess the effects of myosin inhibitors compared to usual care or placebo in people with HCM in the following population subgroups.

1. By demographics, such as age and sex
2. Obstructive HCM versus non-obstructive HCM
3. Genotype-negative and genotype-positive disease
4. People with and without pre-existing atrial fibrillation or other types of arrhythmias

BACKGROUND

Description of the condition

Hypertrophic cardiomyopathy (HCM) is a common myocardial disorder, affecting an estimated 20 million people worldwide [1]. Approximately 30% to 40% of individuals with HCM have pathological variants in genes encoding cardiac sarcomere proteins [2]. These cases with known sarcomeric mutations predominantly follow an autosomal dominant inheritance pattern, though some arise sporadically as new mutations (de novo) [3]. Autosomal recessive inheritance has been observed, but occurs considerably less frequently [4].

In these inherited forms of HCM, disease penetrance is incomplete, and expression varies widely between individuals [5]. Some people with known causal variants may never develop the HCM phenotype, while in others it manifests as subclinical disease or overt HCM [6]. For the remainder of people who develop the disease phenotype but where no pathogenic variant is identified, they are classified as having genotype-negative HCM. A subset of genotype-negative cases, called non-familial HCM, lacks both identifiable pathogenic variants and evidence of HCM in a first-degree relative. This non-familial subtype accounts for around 40% of HCM probands [7, 8].

People with HCM are at risk of progressive heart disease, including loss of ventricular function, ventricular arrhythmia, atrial fibrillation, heart failure, and sudden cardiac death. Based on the degree of left ventricular outflow tract obstruction, HCM is classified as obstructive (oHCM) or non-obstructive (nHCM). Although nHCM was originally considered to follow a relatively benign clinical course, the risk of heart failure is still elevated compared to the general population, with advanced heart failure (New York Heart Association (NYHA) class III/IV) developing in at least 10% of people [9, 10]. Furthermore, people with nHCM appear to be at an even higher risk of developing arrhythmias, such as atrial fibrillation or malignant ventricular arrhythmias, compared to people with oHCM [11].

Description of the intervention and how it might work

Heart muscle contraction is driven by cross-bridge formation between myosin and actin filaments within the sarcomere. Adenosine triphosphatase (ATPase) catalyses the release of energy stored in adenosine triphosphate (ATP), causing the actin-myosin cross-bridges to shorten, leading to contraction of the heart muscle [12]. This process is regulated by various proteins, including cardiac myosin-binding protein C. In ventricular tissue, the β-cardiac isoform is the predominant form of myosin expressed [13].

Although many causal genes for HCM have been identified, about half of the HCM cases with a known genetic basis are due to mutations in genes encoding the heavy chain of β-myosin (*MYH7*, Ensemble identifier: ENSG00000092054) or myosin binding protein C (*MYBPC3*, Ensemble identifier: ENSG0000013457) [14]. These mutations are associated with much higher than normal ATPase activity [12, 15], which results in the increased sarcomere contractility in HCM [15].

Myosin inhibitors are a novel class of medications specifically developed for the treatment of HCM. They are the first disease-modifying therapy for HCM, providing people with a pharmacological alternative to symptomatic management alone. Myosin inhibitors have the potential to reduce the need for invasive cardiac procedures — such as septal reduction therapy for people with oHCM — which carry risks of complications and require long recovery times. They could be particularly beneficial for people who are unable to access septal reduction therapy due to resource limitations, for those with comorbidities that increase the risks associated with septal reduction therapy, or for those who do not wish to undergo septal reduction therapy [16].

Mavacamten, the first in its class myosin inhibitor, binds reversibly to the heavy chain myosin in cardiomyocytes, shifting myosin heads from the disordered to the super-relaxed state. This reduces the rate of myosin-actin cross-bridge formation, ultimately decreasing cardiac hypercontractility [17, 18]. Aficamten, the second myosin inhibitor to be developed, is also thought to reduce myosin-actin cross-bridge formation but does so through allosteric inhibition of myosin ATPase at a different binding site, independent of the super-relaxed state-mechanism [18].

In animal models, these drugs have been shown to reduce cardiac sarcomere hypercontractility [19, 20], resulting in a reduction in cardiomyocyte disarray and prevention of ventricular hypertrophy with mavacamten [20], and reduced left ventricular pressure gradients with aficamten [21]. Inhibition of ATPase activity is also thought to reduce diastolic stiffness and reduce myocardial energy consumption [22]. These improvements in cardiac metrics are anticipated to alleviate symptoms of heart failure, reduce mortality, and delay or even reverse disease progression in people with HCM.

These two myosin inhibitors, mavacamten and aficamten, are in the clinical phase of testing. Mavacamten has already received marketing approval in the US based on its short-term beneficial effects on function capacity in people with oHCM with a NYHA class II or III. Both compounds are currently in phase III trials exploring long-term effects on clinical outcomes such as atrial fibrillation, heart failure, and sudden cardiac death, as well as to explore effectiveness in people with nHCM [23, 24], and people with genotype negative disease [25].

Why it is important to do this review

Before the approval of mavacamten by the US Food and Drug Administration (FDA) in 2022, treatment for HCM focused on symptom relief and managing heart failure complications. By targeting the fundamental disease processes, myosin inhibitors may offer a more direct approach to the management of HCM. They could potentially be used as a monotherapy (e.g. to prevent or delay progression in presymptomatic disease), or in combination with traditional management of cardiovascular risk and heart failure symptoms later in the disease course.

Early clinical trials for mavacamten have shown promising results across both symptomatic and functional endpoints in people with oHCM. The PIONEER-HCM [26], EXPLORER-HCM [27], and EXPLORER-CN [28] trials have demonstrated mavacamten's effectiveness in improving NYHA functional capacity, exercise capacity, left ventricular outflow tract obstruction, self-reported quality of life, and certain heart failure biomarkers, such as N-terminal pro B-type natriuretic peptide (NT-proBNP) and high-sensitivity cardiac troponin I (hs-cTnI). Studies have reported beneficial effects for individuals with advanced disease (NYHA class III/IV), including a reduced need for septal reduction therapy. These positive effects also have been observed over longer follow-up periods [29].

Aficamten has also shown encouraging results in people with symptomatic oHCM. The initial phase II (REDWOOD-HCM) and phase III trials (SEQUOIA-HCM) have demonstrated aficamten's safety [30], and its effectiveness in increasing exercise capacity, measured by peak oxygen uptake (pVO_2) during cardiopulmonary exercise testing [31]. Similar to findings of the mavacamten studies, the benefits of aficamten have been observed across many of its trials' secondary endpoints, such as improvements in functional capacity as measured by Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score (KCCQ-CSS) [32] and NYHA class, reduction in left ventricular outflow tract obstruction, as well as less need for septal reduction therapy.

Beyond their effects in oHCM, trials have shown promising results for both mavacamten and aficamten in people with nHCM [33, 34]. These findings indicate that myosin inhibitors may be an effective treatment option for both types of HCM.

Current evidence from systematic reviews

Fifteen reviews have investigated the effect of myosin inhibitors for HCM [35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49]. Out of these, 13 conducted meta-analyses and two did not [35, 42]. No Cochrane reviews have been published in this area, and the existing systematic reviews and meta-analyses have several limitations.

1. Available reviews predominantly focused on trials with a short treatment duration.
2. Four reviews meta-analysed aficamten trials together with results from a larger set of mavacamten trials [46, 47, 48, 49], skewing results towards the effects of mavacamten.
3. Existing reviews have not specifically investigated the effect of myosin inhibitors on people with nHCM.
4. These reviews did not adequately consider potential differences in the effect of myosin inhibitors between genotype-negative and genotype-positive HCM.

These systematic reviews frequently lacked prespecified protocols, many did not report the search strategy used to identify potentially eligible studies in sufficient levels of detail, and some did not evaluate the quality of the evidence being assessed appropriately. For example, reviews combined studies of varying levels of quality (e.g. including both parallel trials and cross-over trials [45]) into a single meta-analysis.

Furthermore, there are clinical questions that have not been addressed in either the individual studies or the existing systematic reviews. For example, atrial fibrillation and other arrhythmias are known to accelerate progression of ventricular dysfunction and cardiac hypercontractility in people with HCM but no studies have evaluated whether myosin inhibitors have different effects in those with pre-existing atrial fibrillation and other arrhythmias compared to those without [50]. Additionally, given their effects on cardiac myosin ATPase, it is currently unclear to what extent the effectiveness of myosin inhibitors is modified by HCM mutations in non-myosin genes, and how effective this drug class is in people with genotype-negative HCM. Studies in human cardiac tissue have shown that myosin head conformation is unaltered in people with genotype-negative HCM [51], and retrospective studies have found that the effects of myosin inhibitors are attenuated for people with genotype-negative HCM compared to genotype-positive disease [52]. While a subcohort analysis of the SEQIOUA-HCM trial is planned to investigate the effects of aficamten in people with genotype-negative and genotype-positive HCM [53], a comprehensive evaluation of the effectiveness of myosin inhibitors across patients with different genetic profiles is needed.

Given the above limitations, it is important to conduct a Cochrane review on this topic. This Cochrane review will include recently published results, such as those from the SEQUOIA-HCM trial [31], which will provide a better understanding of the compound-specific effect profile of myosin inhibitors, as well as their effectiveness in nHCM. Additionally, several ongoing trials (ODYSSEY-HCM [23], MAPLE-HCM [24], and ACACIA-HCM [54]) with longer follow-up times, more data on aficamten, and more data on nHCM, will be included in this review or in future updates. This Cochrane review will help guide clinical practice by evaluating evidence for distinct patient groups (nHCM/oHCM, people with genotype-negative HCM), longer-term follow-up, potential compound-specific effects, as well as determining the certainty of the evidence using GRADE [55].

OBJECTIVES

Primary objective

To assess the effects of myosin inhibitors compared to usual care or placebo on exercise capacity, need for septal reduction therapy, and all-cause mortality in people with hypertrophic cardiomyopathy (HCM).

Secondary objectives

To assess the effects of myosin inhibitors compared to usual care or placebo in people with HCM in the following population subgroups.

1. By demographics, such as age and sex
2. Obstructive HCM versus non-obstructive HCM
3. Genotype-negative and genotype-positive disease
4. People with and without pre-existing atrial fibrillation or other types of arrhythmias

METHODS

We will follow the Methodological Expectations for Cochrane Intervention Reviews (MECIR) when conducting the review [56], and PRISMA 2020 for the reporting [57, 58].

Criteria for considering studies for this review

Types of studies

We will include parallel group randomised controlled trials (RCTs). We will exclude quasi-randomised trials, including those using quasi-randomised allocation strategies, such as randomisation by alternation, day of the week, or social security/hospital record number [59]. We will exclude factorial, cross-over, and cluster-RCTs, as well as non-randomised trials.

In addition to full-text studies, we will consider studies reported as abstract only and unpublished data for inclusion. We will include eligible studies regardless of outcomes reported. If a trial is potentially eligible for inclusion but is missing relevant data needed to make a decision about eligibility, we will contact the study authors to request the necessary information.

Types of participants

We will include trials that randomised adults (aged 18 years or older) with HCM irrespective of the underlying aetiology, which were conducted in both inpatient and outpatient settings.

We will exclude trials considering myosin inhibitor therapy for people with conditions other than HCM, such as for the treatment of heart failure in general. We will also exclude trials of participants with a diagnosis of diseases that can mimic HCM, such as Fabry disease or amyloidosis.

In cases where only a subset of participants in a study are eligible for inclusion, we will contact the study authors to request the relevant data.

Types of interventions

We will include RCTs that compare oral administration of a specified dose of a myosin inhibitor (e.g. mavacamten or aficamten) with either placebo, active comparison interventions (e.g. beta-blockers), or usual care. Specifically, we will include any of the following comparisons.

1. Myosin inhibitor plus usual care compared to placebo plus usual care
2. Myosin inhibitor plus usual care compared to usual care only
3. Myosin inhibitor plus usual care compared to active comparison plus usual care
4. One myosin inhibitor compared to a different myosin inhibitor (e.g. mavacamten versus aficamten, or comparisons involving myosin inhibitors developed in the future)

We will not impose restrictions on dosages or dosing frequencies. Dosing of myosin inhibitors may need to be titrated on an individual basis, according to a person's left ventricular ejection fraction and left ventricular outflow tract pressure gradient [17]. Usual care includes management of symptoms or complications of HCM (e.g. heart failure) with mono- or combination therapy with beta-blockers, non-dihydropyridine calcium channel blockers, disopyramide, or ranolazine. We will document all available information in relation to the dosage, frequency, and duration of treatment that is reported in the included trials.

We will investigate the effects of each myosin inhibitor individually in the primary analysis. As a sensitivity analysis, we will pool the effects of myosin inhibitors to estimate a possible overall class effect.

Outcome measures

Critical outcomes

There are no core COMET [60] outcomes for myosin inhibitors or HCM. We will include the following critical outcomes.

1. Change in exercise capacity, measured by peak oxygen uptake (pVO_2) on cardiopulmonary exercise testing
2. Need for septal reduction therapy
3. All-cause mortality

We will explore these objectives separately for each myosin inhibitor. For pVO_2, we will calculate the change between baseline measurements and the latest available measurement. If outcomes are reported more than once during follow-up, we will select the latest available data point. For example, if measurements are available at 24 and 36 weeks, we will use the data at 36 weeks. We will use meta-regression to investigate the relationship between maximum follow-up time and myosin inhibitor effect size across trials.

The trials included in this review may not assess outcomes over important time frames. Therefore, this review will also identify gaps in the literature and highlight these areas to guide future research.

Important outcomes

1. Change in left ventricular outflow tract pressure gradient
2. Change in NYHA classification
3. Change in HCM symptoms
4. Hospitalisations due to heart failure
5. Malignant ventricular arrhythmias
6. Atrial fibrillation

We will evaluate the change in left ventricular outflow tract pressure gradient at rest and after provocation (Valsalva manoeuvre or exercise). We will assess a change in HCM symptoms using responses from either the KCCQ-CSS [32] or the Hypertrophic Cardiomyopathy Symptom Questionnaire Shortness-of-Breath (HCMSQ-SoB) [61].

For left ventricular outflow tract gradient, NYHA classification, and HCM symptoms, we will calculate the change between baseline measurements and the latest available measurement.

Search methods for identification of studies

We will apply no publication (published, unpublished (those that are not published in a peer-reviewed journal), or ongoing), study location, or language limitations.

As the first preclinical studies for mavacamten as a potential treatment for HCM were published in 2016 [20], we will limit our search to studies conducted from 2015 onwards.

We will ensure that the analysis is no longer than 12 months old. If this time frame is exceeded, the search will be rerun to investigate if any more studies meet the criteria for inclusion.

Electronic searches

We will search the following electronic databases for published studies:

1. Cochrane Central Register of Controlled Trials via the Cochrane Library (CENTRAL; latest issue)
2. MEDLINE Ovid
3. Embase Ovid

We will use the Cochrane Highly Sensitive Search Strategy to identify randomised trials in MEDLINE and Embase [62]. See Supplementary material 1 for the MEDLINE search strategy. We will adapt this search strategy for use on other databases. We will report the final search strategy for each database.

Searching other resources

We will search the reference lists of the trials included in the review, and any previous review articles on this topic, for potential RCTs.

To improve our chances of finding unpublished studies, we will search the following resources.

1. ClinicalTrials.gov
2. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) Search Portal
3. Medical regulatory agency websites, such as:
   a. US FDA website
   b. UK's Medicines and Healthcare products Regulatory Agency (MRHA) Yellow Card reports
   c. European Medicines Agency (EMA)
   d. Japan's Pharmaceuticals and Medical Devices Agency (PMDA) website
   e. China's National Medical Products Registration website

We will contact trial authors to request further details on incomplete reports, including conference abstracts, as well as information on any unpublished studies. Additionally, we will contact trial authors to request data on important outcomes not already included in the reports, such as genotype data to differentiate genotype-positive versus genotype-negative HCM amongst the study participants.

As only searching published results for adverse events may underestimate adverse events, we will also search for adverse events using published and unpublished studies (including clinical trials registers, clinical study reports, and regulatory agency websites) [63]. We will record the number of unpublished studies found and note any cases where data on adverse effects were unavailable [63].

Data collection and analysis

Selection of studies

We will remove duplicates generated during the search using CRS-Web [64]. Two review authors (SQ and AFS) will conduct a pilot test using six to eight articles to evaluate the study eligibility criteria. Based on any issues identified during this pilot phase, we will refine our search strategy as needed before proceeding.

Unpublished studies will undergo assessment using the same eligibility criteria as published studies (see Criteria for considering studies for this review). We will contact authors of unpublished studies when available data are insufficient to determine eligibility [65]. We will exclude studies if we cannot obtain necessary eligibility information.

Two review authors (SQ and AFS) will independently screen all the search results, starting with the study titles and abstracts. We will then review the full text of any studies identified as potentially relevant. We will resolve any disagreements through discussion, and, if necessary, consult a third review author (AA), who will adjudicate. We will provide a PRISMA flow diagram of trial selection. We will list the reasons for excluding studies during the full-text assessment in the 'Characteristics of excluded studies' table [57]. We will combine multiple reports of the same RCT into a single trial identifier to ensure that each RCT, rather than the individual report, is the unit of analysis in the review.

Data extraction and management

Two review authors (SQ and AFS) will independently use a standardised data collection form to extract the outcome data and study characteristics from the included studies. This form will first be piloted on at least one trial. We will attempt to resolve any disagreements though discussion, and, if necessary, consult a third review author (AA) for adjudication. We will gather sufficiently detailed data on the characteristics of each eligible study to complete the 'Characteristics of included studies' table.

We will extract the following data from studies.

1. **Study characteristics:** study title; study type; year of publication; whether the trial protocol is available; number of centres or countries involved; and sponsorship or funding sources.
2. **Methods***:* study design; recruitment start and end dates; and number of participant withdrawals after randomisation.
3. **Participants:** number of randomised participants and participant-level characteristics (including age, sex, NYHA class, oHCM/nHCM, HCM genotype status, pre-existing atrial fibrillation or other types of arrhythmia).
4. **Interventions and comparisons:** dose, timing, and frequency of active intervention arm (myosin inhibitor) and comparator (placebo or active comparator or alternative myosin inhibitor), as well as the background usual care received in both arms.
5. **Outcomes:** at the latest available follow-up time periods available, as detailed in the Outcome measures section.
6. **Other:** number of participants lost to follow-up; study ethics committee approvals and the trial registration number; inclusion and exclusion criteria; author conflicts of interest, with help from tools such as the Tool for Addressing Conflicts of Interest in Trials (TACIT) [66, 67].

Where appropriate, we will extract cell frequencies, means or medians as well as standard deviations, point estimates (i.e. mean difference (MD), odds ratio (OR)), and standard errors.

One review author (SQ) will upload the final data into Review Manager software [68]. A second review author (AFS) will check the data against the original study reports.

Risk of bias assessment in included studies

Two review authors (SQ and AFS) will independently evaluate the risk of bias for each outcome using the Cochrane RoB 2 tool [69], following the guidelines in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* [70]. We will resolve any disagreements through discussion, and, if necessary, consult a third review author (AA) for adjudication. We will retrieve expressions of concern, errata, corrigenda, and retractions to ensure that any postpublication amendments are considered when determining study eligibility and risk of bias assessments [71].

We will assess the following biases for outcomes.

1. Bias arising from the randomisation process
2. Bias due to deviations from intended interventions
3. Bias due to missing outcome data
4. Bias in measurement of the outcome
5. Bias in selection of the reported result

We will include the following critical and important outcomes in the summary of findings table.

1. Change in exercise capacity measured by pVO_2 on cardiopulmonary exercise testing
2. Need for septal reduction therapy
3. All-cause mortality
4. Change in left ventricular outflow tract pressure gradient
5. Change in HCM symptoms
6. Hospitalisations due to heart failure
7. Malignant ventricular arrhythmias

We will assess the above outcomes at the maximum follow-up reported for that outcome.

We will evaluate potential biases using the signalling questions of the RoB 2 tool. For each domain, we will categorise the risk as high, some concerns, or low, based on the responses to these questions. We will create a visual summary of our risk of bias assessments and, where feasible, incorporate this information into our meta-analysis forest plots. Our assessment of the overall risk of bias will err on the side of caution; we will consider the highest risk of bias in any one domain to be the risk of bias for the study overall [69]. However, if we note 'some concerns' of bias across multiple domains, then we will consider a high overall risk of bias. These findings will inform our GRADE assessment.

We will focus on intention-to-treat results when investigating the effects of intervention on the outcomes. For adverse events, we will extract data from intention-to-treat groups, and from per-protocol and as-treated groups if these data are available.

Measures of treatment effect

We will report dichotomous outcomes using odds ratios, hazard ratios, risk ratios, or risk differences, with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale, we will report mean differences with 95% CIs. When trials use different scales to measure the same outcome, we will use standardised mean differences with 95% CIs [72].

Historically, a 5-point change in KCCQ-CSS was used to identify a clinically important difference in treatment effects [73]. However, recent work has found that even smaller changes in KCCQ-CSS can indicate clinically significant differences [74]. Therefore, we will consider a change of 4 points or more across all domains of the KCCQ-CSS to be clinically significant.

Unit of analysis issues

This review will only consider parallel-arm RCTs as eligible for inclusion. Therefore, we do not anticipate any unit of analysis issues related to alternative trial designs, such as cluster or cross-over trials. We also do not anticipate encountering any multiple-arm studies. However, in RCTs that do compare three or more groups, we will use a pairwise comparison of participants to avoid omission or double counting as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* [72]. For example, in a study with three intervention groups (e.g. a myosin inhibitor, an active comparator (such as a beta-blocker), and a placebo), we would combine participants from the 'active comparator' and 'placebo' groups into a single group. This new group would be compared with the group that received a myosin inhibitor in the usual manner [75].

Dealing with missing data

We will contact the trial authors to request missing or unreported data (including genotype data for HCM risk loci), to clarify unclear information, and to verify outcome data or important details of the study. Additionally, we will record the number of participants lost to follow-up or dropouts for each study.

If we cannot obtain the missing data from study authors, we will describe the details and extent of this for each study in the risk of bias table and discuss their possible impact on the interpretation of the results. Additionally, we will conduct sensitivity analyses to examine the influence of missing data, which will exclude studies identified at high risk of bias due to missing outcome data.

Reporting bias assessment

If more than 10 studies are included in the analyses, we will create a funnel plot for the primary outcome to assess potential asymmetry. We will use a formal statistical test, such as Egger's test, to evaluate asymmetry [76]. We will investigate small-study effects and non-reporting biases as possible explanations for any observed asymmetry. Additionally, we will consider other potential sources of asymmetry, including true heterogeneity, artefactual causes, and chance [77].

To assess outcome reporting bias, we will compare results from trial protocols with their published reports to detect selective reporting. If a result is missing, we will use the Outcome Reporting Bias in Trials (ORBIT) system [78], and assess if its absence is related to the P value, or magnitude or direction of the result [77].

Synthesis methods

As there is potential for the effect of the myosin inhibitors to vary across study populations, we will pool outcome data using the inverse variance method for random-effects meta-analysis using Review Manager [68, 79]. This includes mean differences (or standardised mean differences for continuous outcomes), risk ratios, odds ratios, or hazard ratios.

Investigation of heterogeneity and subgroup analysis

Investigation of heterogeneity

We will evaluate the statistical heterogeneity of effect estimates amongst the included studies by visually examining forest plots and calculating both the Chi^2 test and the I^2 statistic to estimate the percentage of heterogeneity not due to sampling error [79].

In addition to statistical heterogeneity, we will consider heterogeneity between studies based on clinical diversity of the study participants and methodological diversity of the included studies [79]. To assess clinical heterogeneity, we will compare participant characteristics, the dose and type of interventions administered, and the outcomes measured across the eligible studies. Similarly, we will assess methodological heterogeneity by comparing study methods (e.g. study design), and through risk of bias assessments. We will only progress to conducting a meta-analysis if the studies are sufficiently similar in terms of clinical and methodological variation to produce a useful summary. If there is significant heterogeneity that may be a result of unforeseen clinical heterogeneity, we will attempt a post-hoc subgroup analysis, and we describe our rationale for including this additional analysis. If we cannot conduct a meta-analysis due to heterogeneity, we will present the results in a narrative synthesis following the Synthesis Without Meta-analysis (SWiM) reporting guideline [80]. Additionally, we will adhere to Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* for presenting findings using other methods such as visually displaying data with forest plots without summary estimates [81].

Subgroup analysis

We will conduct subgroup analysis on the following characteristics that may introduce clinical heterogeneity.

1. Age, due to higher risk of disease progression in middle age, defined as 40 years or older at enrolment [82]
2. Sex (men versus women), as risk of disease progression may be higher in women than in men [83]

Given the diverse clinical phenotypes of HCM, we will also conduct subgroup analyses to compare the effectiveness of myosin inhibitors according to:

1. HCM type (oHCM versus nHCM);
2. genotype-positive versus genotype-negative HCM (i.e. determined by the presence or absence of a confirmed pathogenic or likely pathogenic gene variant);
3. people with and without pre-existing atrial fibrillation or other types of arrhythmia.

We will utilise interaction tests to evaluate variations in treatment effects between subgroups [84]. For the primary analysis, we will apply the significance test described by Borenstein and Higgins using random-effects models [85]. If we identify any additional characteristics that appear important for subgroup analysis, we will include them post-hoc and document our decision.

Equity-related assessment

We will not extensively investigate health inequity in this review due to the likely insufficient number of eligible trials that have assessed the effect of myosin inhibitors across various inequality and inequity metrics. Where possible, we will evaluate whether age and sex act as effect modifiers in our subgroup analyses. However, we anticipate that there will not be enough studies that record relevant data in PROGRESS-Plus domains [86], such as ethnicity, socioeconomic status, place of residence, social capital, religion, etc., or enough studies from low- and middle-income countries, to thoroughly examine health inequities.

If we find sufficient studies to explore additional domains of health equity during the analysis, we will include these analyses post-hoc, following the guidance from Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* [87], and document our decision process accordingly.

Sensitivity analysis

As sensitivity analyses, we will include studies that were initially excluded for only reporting outcomes over a short follow-up period (less than 24 weeks), and those which were excluded because of their high risk of bias due to missing outcome data.

Certainty of the evidence assessment

Two review authors (SQ, AFS) will independently use the GRADE approach to evaluate the certainty of the evidence for each outcome, considering factors such as risk of bias, consistency, imprecision, indirectness, and publication bias [88]. In the case of differing GRADE assessments, we will resolve any disagreements through discussion, and, if necessary, consult a third review author (AA) for adjudication. We will present the findings of our review in a summary of findings table.

We will include the following critical and important outcomes in the summary of findings table.

1. Change in exercise capacity measured by pVO_2 on cardiopulmonary exercise testing
2. Need for septal reduction therapy
3. All-cause mortality
4. Change in left ventricular outflow tract pressure gradient
5. Change in HCM symptoms
6. Hospitalisations due to heart failure
7. Malignant ventricular arrhythmias

The time frames will be the maximum follow-up time reported for that outcome. If there are no results available for an outcome at 24 weeks or later, we will not include this outcome in summary of findings table.

We will follow the GRADE checklist [89], and use the definitions provided by the GRADE Working Group [55]. We will document any judgements and justifications about the certainty of evidence in the footnotes of the summary of findings table for each outcome.

The GRADE approach categorises the certainty of evidence into four levels: high, moderate, low, and very low [88].

1. **High certainty:** we are very confident that the true effect is close to the estimated effect.
2. **Moderate certainty:** we believe the true effect is likely close to the estimate, but there is a possibility of a significant difference.
3. **Low certainty:** our confidence in the effect estimate is limited; the true effect may be significantly different from the estimate.
4. **Very low certainty:** we have little confidence in the estimate; the true effect is likely very different from the estimate.

RCTs are categorised as high-certainty evidence but can be downgraded one level for serious limitations or two levels for very serious limitations [88]. We will downgrade the certainty if any of the following are identified.

1. Serious or very serious risk of bias or limitations in study design or implementation (or both)
2. Serious or very serious uncertainty about the directness of evidence
3. Unexplained heterogeneity or inconsistency of results that we deem to be serious or very serious
4. Serious or very serious imprecision of results
5. A high probability of publication bias

Consumer involvement

We have received feedback on the study outcomes and on the readability of the protocol from a relevant patient representative (see Acknowledgements for more details). We will seek further consumer involvement at the full review stage, including on the readability of the plain language summary.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016183.

Supplementary material 1 Search strategies

ADDITIONAL INFORMATION

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Contributions of authors

Conceiving the protocol: SQ, AA, FA, CRB, PE, JVD, AFS.

Co-ordinating the protocol: SQ, AFS.

Designing search strategies: SQ.

Writing the protocol: SQ.

Provided support on the methods, scope, and writing of the protocol: AFS.

Provided peer review and feedback on the protocol: AA, FA, CRB, PE, JVD, AFS.

All the authors have read and approved the final version of the protocol and agree to be accountable for all aspects of the work.

Declarations of interest

SQ: none.

ASA: has acted as a consultant for Bristol-Myers Squibb.

FA: has acted as a consultant for Healthsage BV.

CRB: has acted as a consultant for Tenaya Therapeutics, and has received research funding from the Horstingstuit Foundation.

PE: has acted as a consultant for Sarepta Therapeutics Inc, BioMarin Pharmaceutical Inc, Sanofi and Genzyme US Companies, Myokardia, Novo Nordisk, Affinia Therapeutics, Pfizer, Amicus Therapeutics Inc, AstraZeneca, and Bristol-Myers Squibb. Additionally, PE has participated on a Data And Safety Monitoring for Cytokinetics.

JVD: none.

AFS: none.

Both SQ and AFS confirm that they have no relevant financial interests to declare. They also have not been involved in myosin inhibitor studies. Similarly, neither SQ nor AFS – who are making decisions about study eligibility, data extraction, risk of bias assessment, or GRADE assessments – have been involved in the conduct, analysis, or publication of a study that could be included in the review.

Sources of support

Internal sources

- AFS (contact author), UK

  The contact author is employed by University College London (UCL). The electronic library resources used to complete this protocol were also provided by UCL.

External sources

- None, Other

  None

Registration and protocol

Cochrane approved the proposal for this review in May 2024.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

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