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ORIGINAL RESEARCH

Clinical Trials in Hypertrophic Cardiomyopathy Therapy: A Comprehensive Analysis of Trials Registered in Global Clinical Databases

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Background: With the disappointing results associated with the use of cardiac myosin inhibitors in the treatment of hypertrophic cardiomyopathy (HCM), the development of new therapies in clinical trials for HCM has rapidly increased. We assessed the characteristics of therapeutic intervention in HCM registered on ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP).

Methods: We conducted a cross-sectional, descriptive study of clinical trials for therapeutic intervention in HCM registered on ClinicalTrials.gov and ICTRP.

Results: This study analyzed 137 registered trials. Regarding study designs of these trials, 77.37% were purpose of treatment, 59.12% were randomized, 50.36% were parallel assignment, 45.26% were performed with masking, 48.18% recruited less than 50 participants, and 27.74% were Phase 2 trials. In total, 67 trials were new drug trials, of which 35 drugs were tested in these trials, and 13 trials involved treatment with mavacamten. Of these 67 clinical drug trials, 44.78% of trials involved the study of amines, and 16.42% involved 1-ring heterocyclic compounds. Regarding the NCI Thesaurus Tree, 23.81% of trials involved myosin inhibitors, 23.81% of trials involved drugs belonging to agents affecting the cardiovascular system, and 20.63% were involved in testing cation channel blockers. The drug-target network showed that myosin-7, potassium voltage-gated channel subfamily h member 2, beta-1 adrenergic receptor, carnitine o-palmitoyltransferase 1, and liver isoform were the most targeted pathways of the clinical trials analyzed in the drug-target network.

Conclusion: The number of clinical trials investigating therapeutic interventions for HCM has increased in recent years. Ultimately, recent HCM therapeutic clinical trials generally did not incorporate either randomized controlled trials or masking and were small studies recruiting fewer than 50 participants. Although recent research has focused on targeting myosin-7, the molecular signaling mechanisms involved in the pathogenesis of HCM have the potential to elucidate novel target pathways.

Keywords: clinical trials, obstructive hypertrophic cardiomyopathy, nonobstructive hypertrophic cardiomyopathy, myosin-7, amines, myosin inhibitors

Introduction

Hypertrophic cardiomyopathy (HCM) is a common inherited myocardial disorder that is caused by mutations in the sarcomere genes. HCM is a genetic disorder transmitted as an autosomal dominant trait, with incomplete penetrance and variable expressivity.[1,2] Epidemiological surveys based on echocardiography indicate that the prevalence of HCM is estimated at 1/500 in the general population.[3,4] Further, approximately 20 million people worldwide suffer from HCM, far exceeding initial predictions of disease burden.[2]

As of now, 29 genes have been linked to HCM, and over 1500 mutation sites have been closely associated with the development of the disease.[5] MYH7 and MYBPC3, which encode beta-myosin heavy chain and myosin-binding protein C, are the two most common causative genes, collectively accounting for roughly 40% of all HCM cases.[6–9] Additionally,

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existing research suggests that prevalent metabolic alterations prompted by mutations in the sarcomere genes in cases of HCM predominantly entail a rise in sensitivity to calcium ions (Ca^{2+}) within the sarcomere and impairments in sarcomere energy metabolism, including suboptimal energy usage, and heightened energy requirements.[10,11] Certain metabolic consequences brought on by these metabolic changes include disruptions in Ca^{2+} metabolic disorders,[10,12] malfunctioning of mitochondria,[13,14] and metabolic reconfiguration.[15,16]

The European Society of Cardiology (ESC) has classified HCM into two broad categories.[17] Obstructive hypertrophic cardiomyopathy (oHCM; also known as HOCM), which represents ~70% of HCM, is characterized by left ventricular outflow tract (LVOT) obstruction (LVOTO) and defined as an instantaneous peak Doppler LV outflow tract pressure gradient ≥30 mm Hg at rest or during physiological provocation such as the Valsalva maneuver, standing, or exercise.[18] In contrast, non-obstructive hypertrophic cardiomyopathy (nHCM) does not have significant LVOTO (<30 mm Hg) at rest or with provocation.[19] Regardless of hemodynamic characteristics, sarcomeric gene mutations result in excessive cardiac actin-myosin cross-bridging[20,21] that culminates in impaired myocardial relaxation, hyperdynamic contractile properties, and abnormal compliance that are hallmarks of this disease.[1] Currently, the management of HCM focuses on the alleviation of symptoms, the prevention of sudden cardiac death, and family screening.[17,22] Treatment of HCM symptoms includes: (1) the use of beta-blockers and non-dihydropyridine calcium-channel blockers to relieve obstruction,[17] (2) alcohol septal ablation (ASA) is an effective therapy and the gold standard for patients with LVOTO and drug-refractory symptoms,[23,24] and (3) treatment with a selective allosteric inhibitor of cardiac myosin ATPase to improve exercise capacity, LVOT obstruction, New York Heart Association (NYHA) functional class, and health status.[25–27]

Clinical trials are the most effective strategy for evaluating the efficacy of a drug for a specific disease[28,29] and are a critical step in the successful development of novel effective drugs.[30] Thus, one of the most important aspects of laying the foundation for future clinical practice is analyzing registered clinical trial data. Established in 2006, the WHO International Clinical Trials Registry Platform (ICTRP) is composed of partner regional or national clinical trial registers that upload information on the studies they hold at defined intervals.[31] Currently, the ICTRP is a platform integrating information from primary registries in 17 countries/areas. This platform is free to access, allowing anyone the access to collect information on clinical trials all over the world.[31–33] ClinicalTrials.gov is a public trials registry provided by the US National Library of Medicine and the US Food and Drug Administration, accounting for more than 80% of all studies in the ICTRP.[34] Therefore, to better understand the current research progress in HCM treatment to provide the latest research hotspots to clinicians and researchers, we performed a cross-sectional study to investigate the characteristics of registered trials on ClinicalTrials.gov and ICTRP regarding HCM therapy.

Methods

Search Strategy and Selection Criteria

A cross-sectional, descriptive study of clinical trials for HCM registered on the ClinicalTrials.gov database (https://clinicaltrials.gov) and ICTRP (https://trialsearch.who.int/) was conducted. The trials were obtained from ClinicalTrials.gov and ICTRP using the advanced search function with the search terms "Hypertrophic Cardiomyopathy" for "condition or disease" and the term "Hypertrophic Cardiomyopathy" for "Health Condition or Problem studied" on November 10, 2022. Next, by using the Venny online software (version 2.1, http://bioinfogp.cnb.csic.es/tools/venny), we found the trials common to both ClinicalTrials.gov and ICTRP. All of the identified clinical trials were assessed to obtain records of all studies. Patient inclusion criteria for this study require a diagnosis of HCM consistent with current guidelines from the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology. All intervention studies on control or compression, outcome measures, and time frames for evaluation of outcomes were collected without any limitations or restrictions. The following information and data were extracted: register number, title, study type, conditions, interventions, locations, start date, the status of the trial, study results, study samples, participant ages, primary sponsor, location, primary purpose, phases of each trial, allocation, intervention model, masking, and intervention. All trials were then further subclassified according to their study type. We used descriptive statistics to characterize trial categories, and frequencies and percentages were provided for categorical data. All analyses were performed using Microsoft Excel (Microsoft Office Excel 2010, Microsoft Corporation). Exclusion criteria included: 1) observation studies, 2) study subjects without HCM, and 3) non-human studies (Laboratory Analysis).

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Data Analysis

Descriptive analyses were used to analyze collected data. Values were entered into the cumulative calculation for that region if different sites were analyzed in the same region, and we defined locations spanning two or more continents as global. Categorical data are reported as frequencies and percentages. Correlations were analyzed using Spearman correlation. All of the analyses were executed using SPSS 20.0. *P*-values < 0.05 were considered to be statistically significant.

Results

Screening and Included Trials

The initial search identified 195 clinical trials and 105 clinical trials on HCM registered on the ClinicalTrials.gov database and the ICTRP database, respectively, from January 1, 1990, through November 10, 2022. After excluding duplicate trials, 242 trials remained (Figure 1A), which was reduced to 139 trials after excluding observation trials and relative factors research trials. After carefully reviewing all of the information, two trials not for HCM therapy were excluded. Finally, a total of 137 registered trials were ultimately evaluated (Figure 1B).

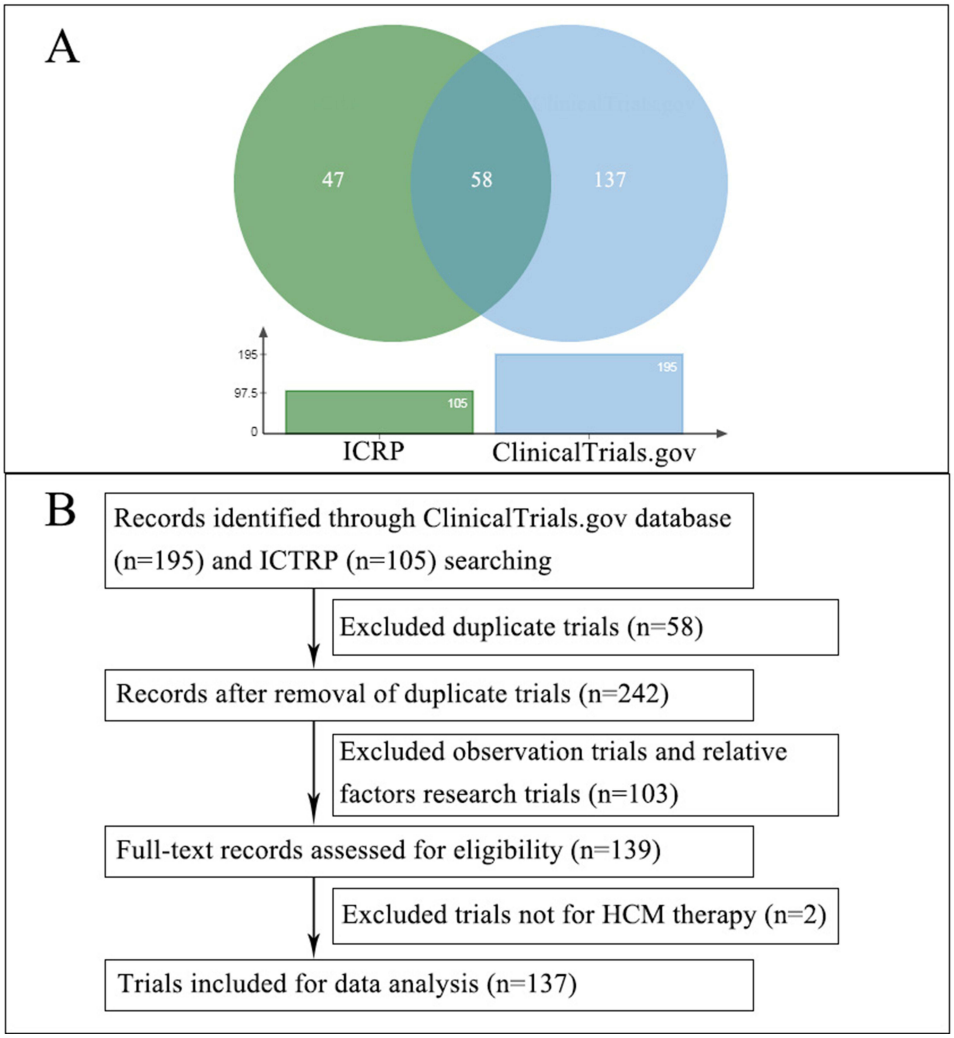

Figure 1 Flowchart of trial selection. (**A**) Venn diagram of the ClinicalTrials.gov database and ICTRP database co-targets. (**B**) Flowchart of inclusion criteria for clinical trial selection. ICTRP, International Clinical Trials Registry Platform.

General Characteristics of Included Trials

Over 80% of trials (117/137; 85.40%) were from ClinicalTrials.gov, which is consistent with previous literature findings.[34] More than half of the trials (72/137; 52.55%) were registered in databases since 2018.

We analyzed to determine whether the number of annual clinical trial registrations included in the study has changed over time. Our analysis, depicted in Figure 2, showed that annual clinical trial registrations increased significantly over time (r = 0.8329, t = 6.8969, p = 8.1494^{e-7} <0.05). A total of 43 trials (31.39%) were completed, followed by those recruiting (28.47%), of unknown status (16.79%), and those active but not recruiting (10.95%). The majority of trials (89.05%) had no results available, with only 15 trials (10.95%) having results reported on ClinicalTrials.gov and ICTRP. Nearly half of trials (49.56%) recruited adults and older adults as study subjects, with 11 trials (8.03%) selecting adult as study participants, and 16 trials (11.68%) enrolling subjects comprising children. In total, 59 trials (43.07%) were performed in Europe, followed by North America (27.01%), Asia (15.33%), and 12 trials (8.76%) performed in greater than or equal to two continents. The characteristics of included trials are shown in Table 1.

Study Designs of Included Trials

The primary purpose of the majority of included trials (77.37%) was treatment, followed by diagnostic (7.30%), not applicable, basic science (4.38%), three trials (2.19%) for screening, three trials (2.19%) for supportive care, and two trials (1.46%) for device feasibility. More than half of allocations were randomized (59.12%), followed by not applicable (29.33%), and non-randomized (10.95%). More than half of the intervention models were parallel assignment (50.36%). A total of 63 trials (45.99%) were performed without masking, 12 (8.76) were with unknown masking, and 62 (45.26%) were performed with masking (12 single maskings, 22 double maskings, 11 triple maskings's, and 17 quadruple maskings). Trial phases were as follows: Phase 1 (8.76%), phase 2 (27.74%), phase 2/Phase 3 (2.92%), phase 3 (8.76%), Phase 4 (8.03%), or not applicable (43.80%). Further, a total of 66 trials (48.18%) recruited less than 50 participants, 34 trials (24.82%) recruited 50–100 individuals, 23 trials (16.79%) recruited 201–500 individuals, 1 trial recruited greater than 500 individuals, and 1 trials did not indicate the number of participants (detailed data are depicted in Table 2).

Overview of Investigated Drugs

A total of 67 trials were involved in clinical drug trials and investigated 35 drugs in 137 intervention trials. Of these 35 drugs, 13 trials involved the drug mavacamten (Figure 3A). We used two major classification systems to

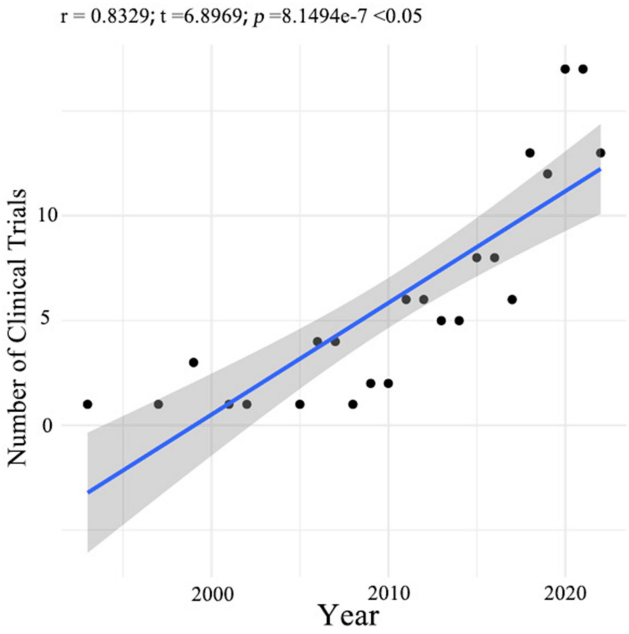

Figure 2 Correlation between the number of trials and beginning year in all 137 included trials.

Table 1 Characteristics of All Included Trials (n = 137)

Variable	Subgroup	N (%)
Source Register		
	ANZCTR	4 (2.92)
	ChiCTR	5 (3.65)
	ClinicalTrials.gov	117 (85.40)
	EU Clinical Trials Register	8 (5.84)
	ISRCTN	1 (0.73)
	JPRN	1 (0.73)
	Netherlands Trial Register	1 (0.73)
Year		
	Prior to 2005	8 (5.84)
	2006–2011	19 (13.87)
	2012–2017	38 (27.74)
	2018–2022	72 (52.55)
Status		
	Active, not recruiting	15 (10.95)
	Authorised	8 (5.84)
	Completed	43 (31.39)
	Recruiting	39 (28.47)
	Suspended	1 (0.73)
	Terminated	5 (3.65)
	Withdrawn	3 (2.19)
	Unknown status	23 (16.79)
Study results		
	Has results	15 (10.95)
	No results available	122 (89.05)
Age group		
	Adult	11 (8.03)
	Adult+Older Adult	109 (49.56)
	Child	1 (0.73)
	Child+Adult	6 (4.38)
	Child+Adult+Older Adult	9 (6.57)
	Not Applicable	1 (0.73)

(*Continued*)

Table 1 (Continued).

Variable	Subgroup	N (%)
Funded by		
	Industry	32 (23.36)
	NIH	7 (5.11)
	Other	77 (56.20)
	Other+Industry	13 (9.49)
	Other+NIH	4 (2.92)
	Not Applicable	4 (2.92)
Locations		
	Africa	1 (0.73)
	Asia	21 (15.33)
	Europe	59 (43.07)
	Global	12 (8.76)
	North America	37 (27.01)
	Oceania	6 (4.38)
	South America	1 (0.73)

Abbreviations: ANZCTR, Australian New Zealand Clinical Trials Registry; ChiCTR, Chinese Clinical Trial Registry; ICTRP, International Clinical Trials Registry Platform; JPRN, Japan Primary Registries Network; NIH, National Institutes of Health.

Table 2 Study Design Elements of Included Trials (n = 137)

Variable	Subgroup	N (%)
Primary purpose		
	Basic Science	6 (4.38)
	Device Feasibility	2 (1.46)
	Diagnostic	10 (7.30)
	Screening	3 (2.19)
	Supportive Care	3 (2.19)
	Treatment	106 (77.37)
	Not applicable	7 (5.11)
Allocation		
	Randomized	81 (59.12)
	Non-Randomized	15 (10.95)
	Not applicable	41 (29.33)

(*Continued*)

Table 2 (Continued).

Variable	Subgroup	N (%)
Intervention model		
	Parallel Assignment	69 (50.36)
	Single Group Assignment	37 (27.01)
	Crossover Assignment	16 (11.68)
	Sequential Assignment	3 (2.19)
	Not applicable	12 (8.76)
Masking		
	Single blind	12 (8.76)
	Double blind	22 (16.06)
	Triple blind	11 (8.03)
	Quadruple blind	17 (12.41)
	None (Open Label)	63 (45.99)
	Not applicable	12 (8.76)
Phases		
	Phase 1	12 (8.76)
	Phase 2	38 (27.74)
	Phase 2+Phase 3	4 (2.92)
	Phase 3	12 (8.76)
	Phase 4	11 (8.03)
	Not Applicable	60 (43.80)
Enrollment		
	<50	66 (48.18)
	50–100	34 (24.82)
	101–200	23 (16.79)
	201–500	12 (8.76)
	>500	1 (0.73)
	Not applicable	1 (0.73)

categorize these 35 compounds: the Medical Subject Headings Classification (MeSH) (https://meshb.nlm.nih.gov/) and the NCI Thesaurus Tree (https://ncit.nci.nih.gov). Of these 67 clinical drug trials, 44.78% of the trials involved amines and 16.42% involved heterocyclic 1-ring compounds (Figure 3B). Of the compounds categorized by the NCI Thesaurus Tree, 23.81% were myosin inhibitors (13 trials for mavacamten and two trials for MYK-224), 23.81% of trials involved agents affecting the cardiovascular system, 20.63% involved cation channel blockers, and 12.70% involved agents affecting nervous system. Of the 15 trials investigating agents affecting the cardiovascular system, 53.33% of trials assessed anti- hypertensive drugs, 20.00% of drugs were classified as not applicable, 13.33% analyzed cardiotonic agents, and 13.33% tested anti- arrhythmic agents (Figure 4).

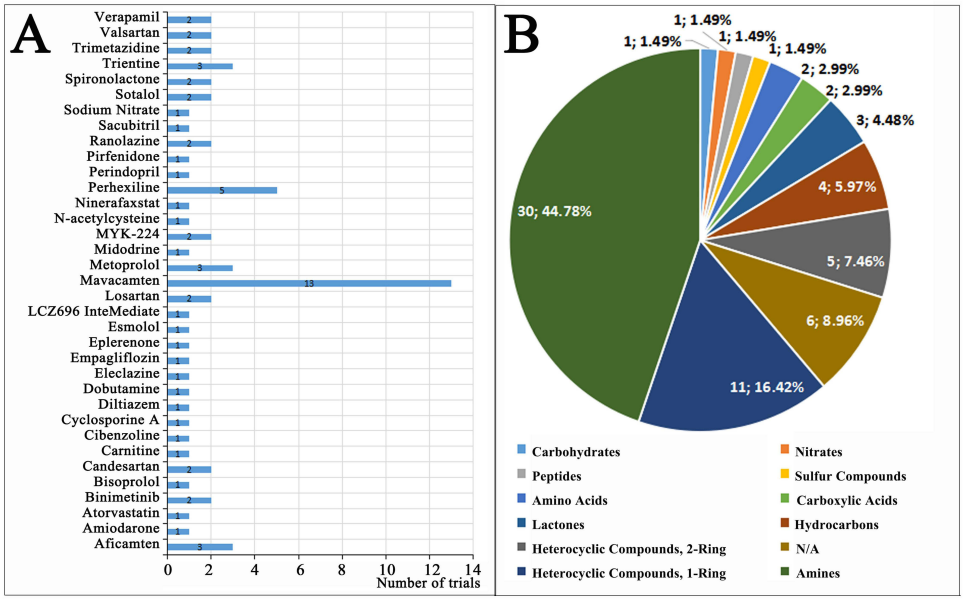

Figure 3 (**A**) Overview of investigated drugs and (**B**) their classification through Medical Subject Headings (MeSH).
Notes: Data from MeSH Tree, https://meshb.nlm.nih.gov/; Mavacamten formerly known as MYK-461; Aficamten formerly known as CK-3773274; Binimetinib formerly known as MEK162; Ninerafaxstat formerly known as IMB-1018972; Vastarel formerly known as Trimetazidine dihydrochloride; TY-0305 formerly known as Cibenzoline.

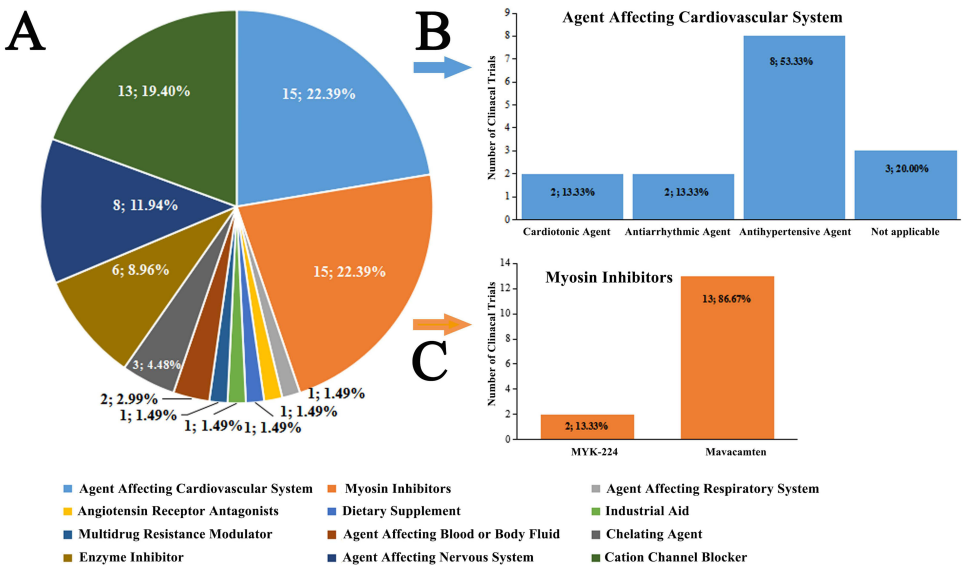

Figure 4 Overview of NCI Thesaurus Tree for investigated drugs. (**A**) Proportion of each classification via NCI Thesaurus Tree; (**B**) Proportion of agents affecting the cardiovascular system; (**C**) Proportion of drugs used as myosin inhibitors.
Note: Data from NCI Thesaurus Tree, https://ncit.nci.nih.gov.

Overview of Investigated Targets

We further identified all 69 targets of the 35 investigated drugs using the DrugBank database (https://go.drugbank.com/). Next, a drug-target network was created and visualized using Cytoscape (Version 3.8.0). The results showed that myosin-7, potassium voltage-gated channel subfamily H member 2, beta-1 adrenergic receptor, carnitine o-palmitoyltransferase 1, and liver isoform were the most targeted proteins of included intervention trials (Figure 5A). The top 10 targets with the maximum number of trials were identified and shown in Figure 5B.

Randomized controlled, masked, and appropriate patient-population trials are critical components of high-quality clinical trials.[35] In further analyzing these 67 clinical drug trials, we narrowed our selection to those registered after 2013,

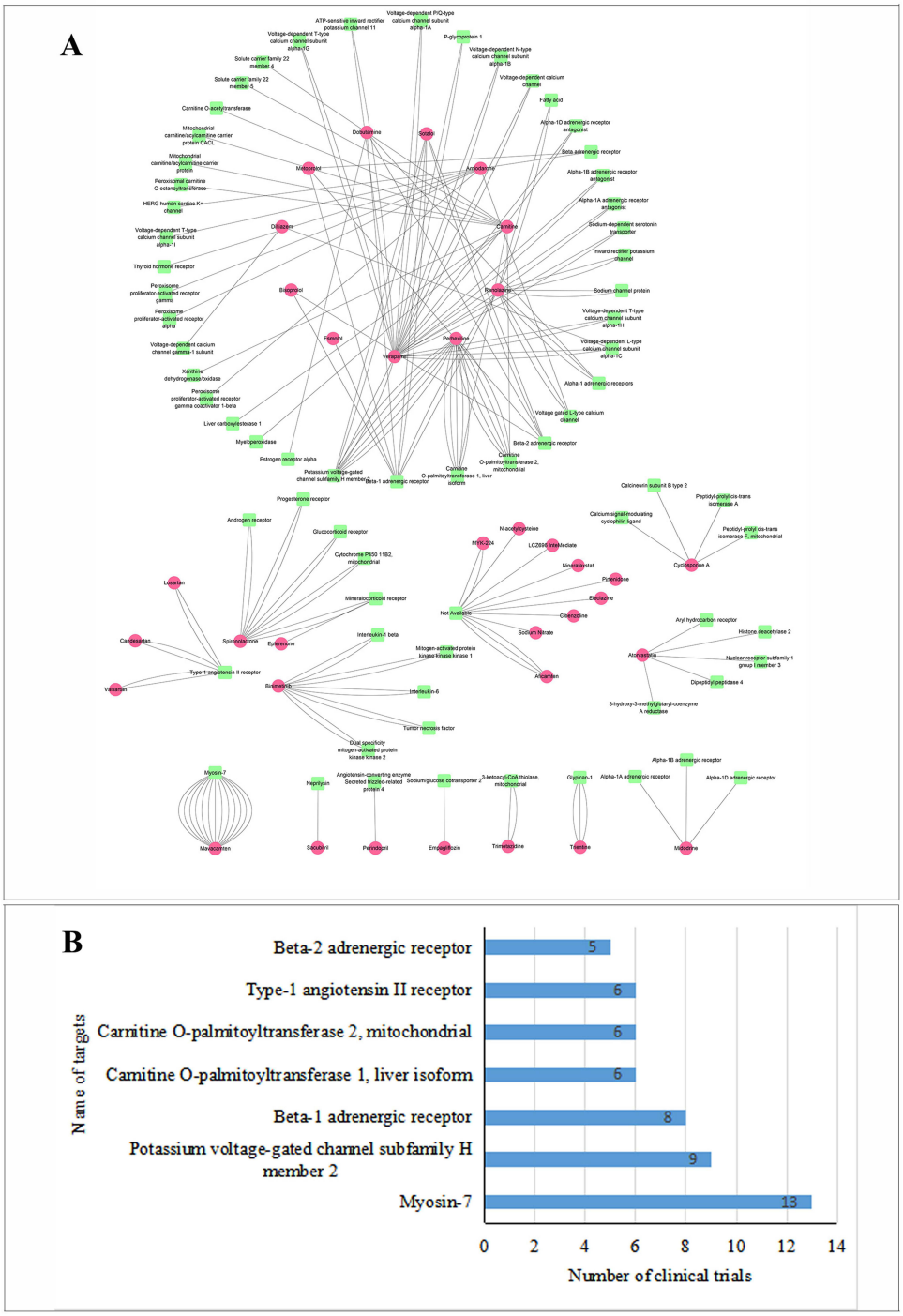

Figure 5 Overview of Investigated Targets. (**A**) Diagram of the formulated drug-target network. (**B**) Graph showing the top seven agents tested in the clinical trials assessed.

excluding trials without randomization, masking, and parallel assignment. This resulted in a selection of 18 trials for further analysis, which is presented in Table 3. Interestingly, of these 18 trials, only four trials were able to complete both recruitment and clinical testing to date. Among these four, three trials were Phase 1–3 clinical trials for mavacamten in the treatment of HCM (NCT02356289, NCT03442764, NCT03470545), and the remaining one was a Phase 2 clinical trial for valsartan in the treatment of early sarcomeric HCM (NCT01912534). The US FDA approved mavacamten on April 28th, 2022, and is now approved for treating symptomatic New York Heart Association (NYHA) class II–III

Table 3 Characteristics of High-Quality Clinical Trials in HCM Therapy

Drug	Trial ID	Recruit Status	Phases	Primary Outcome Measures	US FDA Approval Status	Targets	NCI Thesaurus Tree	Clinical Pharmacology
Mavacamten	NCT02356289	Completed	Phase 1	Incidence of AEs	Approved	Myosin-7	Myosin Inhibitors	• Modulates the number of myosin heads, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation; • Diminishes dynamic LVOT obstruction, leading to improved cardiac filling pressures.[36]
	NCT03442764	Completed	Phase 2	Incidence of AEs				
	NCT03470545	Completed	Phase 3	Clinical response of pVO2 and NYHA functional class				
	NCT03723655	Active, not recruiting	Phase 2/3	Incidence of AEs				
	NCT04349072	Active, not recruiting	Phase 3	Evaluate adults with oHCM who are eligible for SRT.				
	NCT05174416	Recruiting	Phase 3	Valsalva LVOT peak gradient				
	NCT05582395	Not yet recruiting	Phase 3	KCCQ-23 CSS and pVO2				
Trientine	NCT04706429	Authorized	Phase 2	Left ventricular mass indexed to body surface area	Unapproved for HCM; Approved for adult patients with stable Wilson's disease	Glypican-1	Chelating Agent	• Discerning Copper(II) Chelator; • Ameliorates LVH by reducing hypertrophy and fibrosis, improving mitochondrial function and energy metabolism.[40]
Aficamten	NCT04219826	Active, not recruiting	Phase 2	Incidence of AEs	Unapproved for HCM	*Myosin[41]	Myosin Inhibitors	• Exhibits specific and reversible binding to myosin; • Diminishes actin-myosin cross-bridge interactions and decreasing Contractility; • Brings About Reductions In LVOT Gradients.[42]
	NCT05186818	Recruiting	Phase 3	pVO2				

Empagliflozin	NCT05182658	Not yet recruiting	Phase 3	pVO2	Unapproved for HCM; Approved for type 2 diabetes	Sodium/Glucose Cotransporter 2	Enzyme Inhibitor	• Improves Mitochondrial Function; • Reduces LVEF; • Decreases The Risk Of Worsening HF.[43–45]
Esmolol	NCT05073094	Recruiting	Phase 4	The peak concentration of Troponin I	Unapproved for HCM; Approved for short-term use in controlling supraventricular tachycardia	Beta-1 Adrenergic Receptor	Adrenergic Agonist	
Midodrine	EUCTR2015-003521-34-FR	Authorized	Phase 2	Walk distance	Unapproved for HCM; Approved for low blood pressure (hypotension)	Alpha-1A Adrenergic Receptor Alpha-1B Adrenergic Receptor Alpha-1D Adrenergic Receptor	Adrenergic Agonist	Optimizes therapy for HF; Up-titration of neurohormonal antagonist therapy.[46,47]
Ninerafaxstat	NCT04826185	Recruiting	Phase 2	Incidence of AEs	Unapproved for HCM	*3-Ketoacyl Coa Thiolase[48]	Enzyme Inhibitor	Improves myocardial energetic.[49]
Perhexiline	NCT04426578	Recruiting	Phase 2	Change in LVH	Unapproved for HCM	Carnitine O-Palmitoyltransferase 1, Liver Isoform Potassium Voltage-Gated Channel Subfamily H Member 2	Calcium Channel Blockers	Enhanced $p\dot{V}O2$; Improvement in easing diastolic dysfunction during exercise.[50]
Trimetazidine	EUCTR2018-000029-29-NL	Authorised	Phase 2	Myocardial efficiency	Unapproved for HCM; France FDA approved for angina pectoris	3-Ketoacyl-Coa Thiolase, Mitochondrial	Cardiotonic agent	Attenuate the ischemic HF[51]
Valsartan	NCT01912534	Completed	Phase 2	Composite z-score	Unapproved for HCM; Approved for hypertension in adults	Type-1 Angiotensin II Receptor	Antihypertensive agent	Improves the composite Z-Score[52]
LCZ696	NCT04164732	Recruiting	Phase 2	pVO2	Unapproved for HCM	Neprilysin	Angiotensin receptor antagonists	Blood pressure lowering[53]

Note: *The data is not available in the DrugBank database and the NCI Thesaurus Tree but obtained from literature.

Abbreviations: LVEF, left ventricular ejection fraction; HF, heart failure; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; oHCM, obstructive hypertrophic cardiomyopathy; SRT, septal reduction therapy; KCCQ-23 CSS, kansas city cardiomyopathy questionnaire (23-item) clinical summary score; pVO2, peak oxygen consumption; AEs, adverse events.

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obstructive HCM in adults to improve functional capacity and symptoms.[36] Of these 18 trials, 5 clinical trials utilized peak oxygen consumption (pVO2) as their primary outcome measure. It has been recognized that exercise capacity is a prognostic indicator in HCM, and Peak Oxygen Consumption is an independent predictor of survival and outcomes in patients with HCM.[37–39]

Discussion

HCM is a myocardial disease characterized by primary left ventricular hypertrophy, LVOTO, hyperdynamic contractile properties, and diastolic abnormalities.[1,2] Patients with oHCM are often symptomatic and can have atrial fibrillation, heart failure, and malignant ventricular arrhythmias.[2,54] Previously, drug treatment for oHCM focused on symptomatic relief with β blockers, non-dihydropyridine calcium channel blockers, and disopyramide.[17,55,56] However, selective allosteric inhibitors of cardiac myosin ATPase have been widely studied in recent years. Specifically, phase 3 clinical studies were recently completed for mavacamten,[57] and are ongoing for aficamten (CK-3773274) (http://www.chinadrugtrials.org.cn/clinicaltrials.searchlistdetail.dhtml). We analyzed the correlation between the number of trials and the beginning year in all 137 included trials. The number of trials was significantly correlated with the year the trial started ($r = 0.8329$, $P < 0.001$).

Among all 35 drugs, the top 5 in terms of number of registrations included mavacamten (13 trials), perhexiline (5 trials), aficamten (3 trials), metoprolol (3 trials), and trientine (3 trials). Mavacamten is a first-in-class small molecule selective allosteric inhibitor of cardiac myosin ATPase. It was specifically developed to target the underlying pathophysiology of HCM by reducing actin–myosin cross-bridge formation,[57] thereby reducing contractility and improving myocardial energetic potential.[27] Of the 67 trials drugs testing 35 drugs, the top 5 drug types (MeSH Tree) by number of registrations were amines (30 trials), heterocyclic 1-ring compounds (11 trials), heterocyclic 2-ring compounds (5 trials), hydrocarbons (4 trials), and lactones (3 trials). The drug-target network showed that myosin-7, potassium voltage-gated channel subfamily H member 2, beta-1 adrenergic receptor, carnitine o-palmitoyltransferase 1, and liver isoform were the most targeted proteins in the trials analyzed.

Clinical trials are critical to clinical practice and decision-making.[58] Moreover, randomized controlled, masked, and appropriate patient-population trials are critical components of high-quality clinical trials.[35] In our study, more than half of the primary trial purposes were treatment (77.37%), allocations were randomized trials (59.12%), and intervention models were parallel assignment (50.36%). Altogether, 54.75% of the trials were performed without masking, 43.80% of trials were without application of phases, and 48.18% of trials recruited less than 50 participants. There was a certain gap between the majority of clinical trials in this study and high-quality clinical trials. The main reason for this finding is that phase 3 or phase 4 trials only accounted for 16.79%. Further, before the approval of mavacamten, HCM was mainly treated by surgery, which was only performed in a small number of hospitals worldwide.

There are a number of limitations to this study. First, we could have missed some clinical trials whose protocols had not been registered on ClinicalTrials.gov and ICTRP and may instead have been registered in other countries clinical trial platforms, such as the Chinese Clinical Trial Registry Platform (http://www.chictr.org.cn/searchproj.aspx). In addition, we note that several new compounds are lacking MeSH, NCI Thesaurus Tree, and targets, thus limiting our analysis and potentially biasing our estimates by limiting the generalizability of our findings.

Currently, mavacamten and aficamten are the most promising drugs to treat HCM, having significant therapeutic effects. Although both are cardiac myosin inhibitors, they differ slightly in their pharmacological properties. For instance, mavacamten takes longer to reach steady-state blood drug concentrations (6 weeks) and has a sustained pharmacological effect even after discontinuation.[25,59] On the other hand, aficamten reaches steady-state blood drug concentrations more quickly (2 weeks) and has reversible effects after discontinuation.[41] As more clinical trial data accumulates, we will have a better understanding of the differences between these drugs and their optimal application in the treatment of HCM. As the clinical trials for mavacamten are ongoing globally, experimental outcomes related to it have been released consistently. Some studies have demonstrated mavacamten has significantly reduced the fraction of patients with oHCM who meet the guideline criteria for septal reduction therapy (SRT) after 16 weeks. Furthermore, LVOT obstruction has significantly decreased after treatment, along with a marked improvement in the quality of life.[60] In addition, a long-term clinical trial (PIONEER-OLE) was conducted 6–18 months after completion of PIONEER-HCM

and has found that mavacamten is still effective in reducing LVOT obstruction, improving symptoms, and maintaining normal LVEF levels in patients.[61]

The US FDA approved the use of mavacamten in April 2022. The "WARNINGS AND PRECAUTIONS" notice mentions that mavacamten may reduce systolic contraction and has the potential to cause heart failure or obstruct ventricular function. Patients who experience a serious intercurrent illness or arrhythmia are at a higher risk of developing systolic dysfunction and heart failure. Mavacamten is primarily metabolized by CYP2C19 and CYP3A4 enzymes. Therefore, concomitant use of mavacamten and drugs that interact with these enzymes may result in life-threatening drug interactions, such as heart failure or a loss of effectiveness.[36]

Conclusions

The number of clinical trials investigating therapeutic intervention for HCM has increased in recent years. The main characteristics of clinical trials for therapeutic intervention in HCM include lack of randomized control, lack of masking, and recruiting less than 50 participants. Amines, myosin inhibitors, and agents affecting the cardiovascular system have been the focus of most current HCM research. With increased research in targeting myosin-7, the molecular signaling mechanisms involved in the pathogenesis of HCM have the potential to elucidate novel pathways and drug targets.

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Disclosure

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