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Authors' Affiliation:
[1]Wrocław Medical University, wyb. Ludwika Pasteura 1, 50-367 Wrocław, Poland
[2]Uniwersytecki Szpiyal Kliniczny nr 1 im Fryderyka Szopena w Rzeszowie, Emergency Room, Fryderyka Szopena 2, 35-055 Rzeszów, Poland
[3]Institute of Medical Sciences, University of Rzeszów, mal. mjr. Wacława Kopisto 2A35-959 Rzeszów, Poland
[4]University of Warmia and Mazury in Olsztyn, ul. Michała Oczapowskiego 2, 10-719 Olsztyn, Poland
[5]Central Teaching Hospital of the Medical University of Lodz, Pomorska 251, 92-213 Łódź, Poland
[6]Institute of Medical Sciences, University of Rzeszów, al. Tadeusza Rejtana 16C 35-959 Rzeszów, Poland
[7]Dolnośląskie Centrum Onkologii, Pulmonologii i Hematologii, Plac Hirszfelda 12, 53-413 Wrocław, Poland
[8]Medical University in Lublin, Al. Racławickie 1, 20-059 Lublin, Poland

***Corresponding author:**
Małgorzata Bacik, Olszyna, ul. Południowa 30, 63-500 Ostrzeszów, Poland,
Email: malgorzata.bacik@student.umw.edu.pl; https://orcid.org/0009-0006-8350-5064

Orcid and contact list:

Małgorzata Bacik	0009-0006-8350-5064 malgorzata.bacik@student.umw.edu.pl
Klaudia Głodowska	0009-0007-4389-0591 klaudia.glodowska@student.umw.edu.pl
Bartłomiej Józef Rdzanek	0009-0003-2629-6081 Bartlomiej.Rdz@gmail.com
Jakub Żelazo	0009-0001-4262-2540 Jakub.Zelazo@onet.pl
Katarzyna Wacławek	0009-0002-0612-7451 katarzyna.waclawek.med@gmail.com
Anna Ciesielka	0000-0002-6949-477X Ciesielka.ania@gmail.com
Aleksandra Rechcińska	0009-0004-9905-8110 a.rechcinska@gmail.com
Kacper Kiereta	0009-0007-6612-8495 kacper.kiereta@student.umw.edu.pl
Zuzanna Cichowska	0009-0001-9597-2587 zuzanna.cichowska@student.umw.edu.pl
Laura Chmielowiec	0009-0005-8435-0044 laurahelenachmielowiec@gmail.com
Kinga Piela	0009-0002-1507-8065 piela.kinga01@gmail.com

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From diagnosis to therapy: Mavacamten as a breakthrough approach in the treatment of hypertrophic cardiomyopathy

Małgorzata Bacik[1*], Klaudia Głodowska[1], Kacper Kiereta[1], Zuzanna Cichowska[1], Kinga Piela[2], Jakub Żelazo[3], Katarzyna Wacławek[4], Aleksandra Rechcińska[5], Anna Ciesielka[6], Laura Chmielowiec[7], Bartłomiej Józef Rdzanek[8]

ABSTRACT

Hypertrophic cardiomyopathy (HCM) is the most often genetically determined heart muscle disease – has very complex etiopathogenesis and considerable phenotypic variability. The article provides an overview of the evolution of our understanding of HCM as well as a summary of the latest knowledge about the molecular and clinical foundations of HCM, especially the role of mutations in genes encoding sarcomeric proteins and their impact on cellular mechanics, and the latest diagnostic methods, which allow more accurate identification of high-risk patients. The main part of the article is focused on mavacamten (selective cardiac myosin inhibitor) as a potential breakthrough in the treatment of symptomatic, obstructive HCM. Conclusions of major clinical trials (EXPLORER-HCM, VALOR-HCM, MAVERICK-HCM) confirm its effectiveness in reducing LVOT gradient and reducing the need for invasive interventions, which highlights the importance of targeted therapies in the context of the future of personalized HCM treatment.

Keywords: hypertrophic cardiomyopathy (HCM), genetic diagnostics, mavacamten, targeted treatment, cardiac myosin inhibitor

1. INTRODUCTION

The term "cardiomyopathy" first appeared in 1957 and was describing diseases of the myocardium not associated with coronary artery pathology. With the progress of medical knowledge and a deeper understanding of pathogenetic mechanisms, this definition has evolved.

In 1968, the World Health Organization (WHO) declared a new classification where cardiomyopathies were understood as "diseases of diverse and often unknown etiology in which the dominant feature is cardiomegaly and heart failure" (Abelmann, 1984). The definition was changed in 1980 to "diseases of the myocardium of unknown cause" (WHO/ISFC Task Force, 1980). Fifteen years later,

it was transformed to "diseases of the myocardium associated with cardiac dysfunction" (Richardson et al., 1996).

The evolution of these definitions is the best example of limited knowledge about the etiology and molecular mechanisms underlying these conditions at the time. Classifications of myocardial diseases are very complex, based on various criteria - etiology, anatomy, physiology, or treatment methods. Despite numerous attempts to create a universal system, categories often overlap, and no classification fully meets the expectations of all specialists.

In 2006, the latest discoveries allowed the American Heart Association (AHA) to revise the approach to defining cardiomyopathies. Their classification describes cardiomyopathies as a heterogeneous group of myocardial disorders marked by cardiac arrhythmias or impaired contractile function. Most often, those features are accompanied by structural abnormalities of the ventricles - hypertrophy or dilation, but these are not absolute criteria. The etiology of cardiomyopathies is often linked to genetic mutations, which may lead to isolated myocardial damage or coexist with generalized systemic disorders. The consequence of said problems can be the cause of progressive heart failure or fatal cardiac events (Maron et al., 2006).

Based on their morphological and functional characteristics, cardiomyopathies are classified into five types - hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular (ARVC), and a nonspecific or unclassified category. The said approach focuses primarily on structural and functional criteria and does not fully consider their etiopathogenesis. Each of the subtypes mentioned has its own distinct pathophysiology, clinical presentation, and disease course, which indicates need for further subclassification within this diverse group of disorders.

The classification of cardiomyopathies proposed by AHA in 2006 was based on their etiology, dividing them into genetic, mixed, and acquired forms (Maron et al., 2006). The European Society of Cardiology (ESC) introduced a parallel classification system in which each major morphological category is further subdivided into familial/genetic and nonfamilial/nongenetic forms (Pinto et al., 2016). The system proposed by the ESC serves as a valuable tool in differential diagnosis, allowing for the consideration of the clinical diversity of cardiomyopathies, many of which have distinct genetic profiles.

2. REVIEW METHODS

The authors searched PubMed, Scopus, and Google Scholar databases using phrases that contain keywords like “hypertrophic cardiomyopathy”, “sarcomeric mutations”, “genetic diagnostics”, “mavacamten”, and “cardiac myosin inhibitor”. We selected studies by title, abstract, and availability. Boolean operators such as “AND” and “OR” were applied to refine and optimize the search results. The final number of studies included in our review is 27. We included only articles written in English from 1984 to 2024. The article screening process adhered to the PRISMA guidelines (Figure 1).

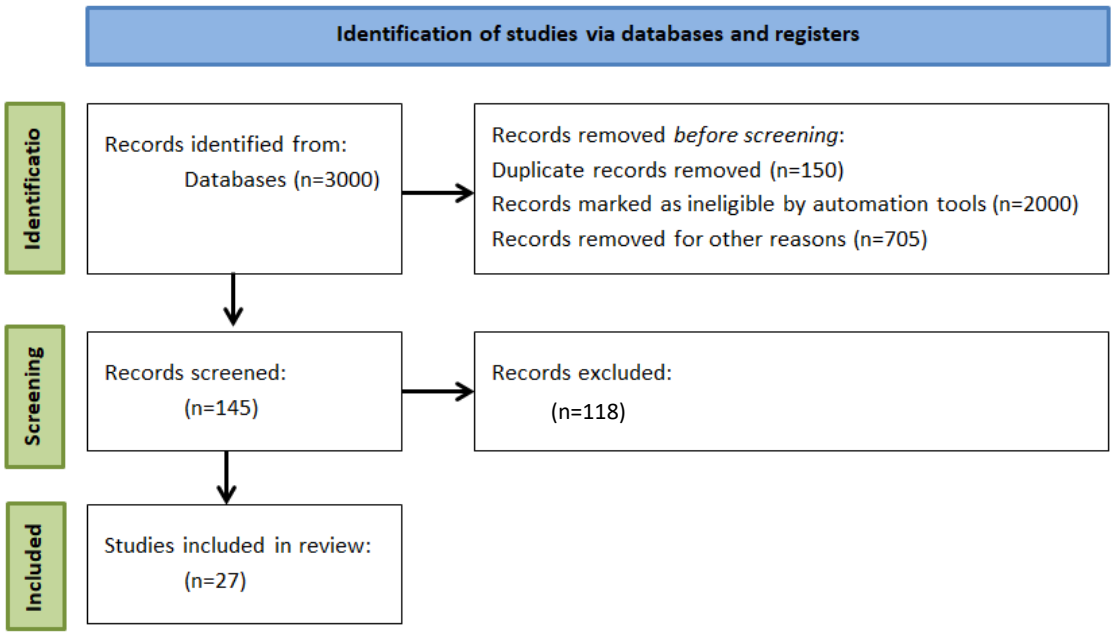

Figure 1. The PRISMA flow diagram shows the process of study identification and screening.

3. RESULTS & DISCUSSION

Epidemiology

HCM is one of the more common myocardial diseases. Current epidemiological reports indicate that its prevalence in the general population reaches 1:200 individuals, which translates to a global number of patients estimated at 15–20 million. Despite such a significant prevalence, HCM remains underdiagnosed, mainly due to the frequent occurrence of paucisymptomatic or asymptomatic forms, subtle morphological changes in the early stages of the disease, imperfections in available diagnostic methods, and limited clinician awareness (Maron et al., 2018).

Pathogenesis and pathophysiology of HCM

HCM is inherited as a monogenic disease in an autosomal dominant manner but de novo mutations are also possible. Genetic studies show that in most patients, heterozygous mutations occur in genes MYBPC3 (myosin-binding protein C), MYH7 (β-myosin), and TNNT2 (troponin T2). In more than 90% of cases, these are missense mutations or mutations leading to the premature appearance of a translation termination codon. Defective sarcomeric proteins that originated from those mutations disrupt the basic function of the contractile unit.

One of the affected aspects is force generation through the interaction of the myosin head with actin filaments and ATP hydrolysis within the catalytic domain. The pathophysiological mechanism primarily consists of increased calcium ion sensitivity and reduced ATPase enzyme activity, which impair interaction between actin and myosin, which hinders the transition of thin filaments to an inactive state at low calcium concentrations. That leads to excessive myocardial contractility (Spudich, 2019). Mutations in the MYBPC3 and MYH7 genes are particularly significant, because they compromise the efficiency of generating the contractile force. Studies indicate that MYH7 variants exert far greater impact on myofibrillar ATPase activity than MYBPC3 mutations. The consequence of these changes is increased energy demand, especially pronounced in MYH7 mutations, and a characteristic reduction in the phosphocreatine-to-ATP ratio in the myocardium observed in HCM (Marian and Braunwald, 2017).

A 2017 study analyzing the genotype-phenotype relationship indicates that patients with HCM caused by MYBPC3 and MYH7 mutations display significantly greater mean interventricular septal thickness compared to those with TNNT2 mutations or idiopathic cases. Clinical observations further confirm that MYH7 mutation cause more pronounced symptomatology and a more severe disease phenotype. This group shows a particularly high incidence of end-stage heart failure and that translates to an increased need for heart transplant eligibility compared to patients with MYBPC3 mutations (Sedaghat-Hamedani et al., 2018).

The mentioned earlier sarcomere increased sensitivity to calcium leads to enhanced cytoplasmic calcium buffering. Furthermore - cellular membrane dysfunction and sarcoplasmic reticulum remodeling occur. Those disturbances directly contribute to electrical remodeling and impaired contractility. As a result, people with HCM are more likely to develop ventricular and supraventricular arrhythmias - the most frequently diagnosed one is atrial fibrillation, with an estimated prevalence of 19–30% (Park et al., 2016).

Sarcomere structure and function anomalies initiate a cascade of cellular reactions that lead to the activation of stress signaling pathways. The most important role is played by growth factors - particularly TGF-β (transforming growth factor beta), calcineurin, and mitogen-activated protein kinases (MAPKs). What stated above results in progressive histological cardiomyocyte disarray, excessive collagen accumulation (interstitial fibrosis), and pathological myocardial hypertrophy (Marian and Braunwald, 2017).

In HCM hypertrophy of myocardium most often is asymmetrical, what is particularly evident in the basal interventricular septum (located below the aortic valve) and the left ventricular free wall. Diagnosis is based on identifying an abnormal septum-to-free-wall thickness ratio (≥1.3:1). An apical variant of HCM, where hypertrophy dominates the cardiac apex, can be observed in fewer cases. Much less frequently, the disease process involves the lateral or posterior left ventricular wall (Marian and Braunwald, 2017; Arbelo et al., 2023).

Pathological hypertrophy combined with fibrosis results in a reduction of heart chamber lumens and increases their stiffness. That impairs contractility and ventricular relaxation capacity. Interventricular septal hypertrophy leads to the obstruction of the left ventricular outflow tract (LVOT). It causes mitral valve leaflets to misplace toward the aorta and potentially can cause valve regurgitation, dynamic outflow obstruction (LVOTO), and elevated intracavitary pressure. As the consequents afterload increases, further aggravating left ventricular hypertrophy (LVH), diastolic dysfunction, and myocardial ischemia (Maron et al., 2006; Arbelo et al., 2023).

Diagnostics

HCM in adults is diagnosed when the thickness of the left ventricular (LV) wall exceeds 15 mm in any segment of the myocardium, noting that it is not purely caused by cardiac loading conditions. In cases where LV wall thickening falls within the 13–14 mm range, additional evaluation of factors such as family history, genetic test results, and ECG is necessary. In first-degree relatives of adults with confirmed HCM, the diagnosis is established at an LV wall thickness of ≥13 mm.

Although most HCM cases are asymptomatic, clinical assessment also plays a significant role in diagnosis. Concerning symptoms include dyspnea, chest pain, episodes of syncope, as well as a positive family history of HCM or sudden cardiac death (SCD) (Arbelo et al., 2023).

Current diagnostic methods (primarily based on two-dimensional echocardiography) have significant limitations. The accuracy of the examination and interpretation of results depends on the quality of the obtained image and the operator's experience. Additionally, this technique may fail to detect minor or focal hypertrophic changes, increasing the risk of missing the disease or misclassifying it (Nagata et al., 2018).

The progress in HCM diagnostics in recent years was possible thanks to the development of advanced imaging techniques that enable precise assessment of myocardial morphology and function. Cardiac magnetic resonance imaging (CMR) provides the most vital clinical information - high-resolution and high-contrast images allow accurate evaluation of the degree of hypertrophy, identification of LVOTO, and detection of myocardial fibrosis through late gadolinium enhancement (LGE) sequences. CMR is often the only reliable method to confirm the diagnosis in cases of HCM with localized hypertrophy (especially in less common locations - the anterolateral free wall or the apex). CMR is also essential to differentiate HCM from other causes of myocardial hypertrophy and to stratify the risk of sudden cardiac death (Maron et al., 2014).

Speckle-tracking echocardiography (STE) is an innovative method that allows to asses the myocardial function. STE analyzes the deformation of muscle fibers during the cardiac cycle. This technique allows to evaluate cardiac mechanics in ways unavailable in traditional echocardiography. STE enables early detection of subclinical myocardial dysfunction, which is particularly important in patients with borderline hypertrophy or inconclusive results from other tests (Geyer et al., 2010).

Employment of genetic testing in the HCM diagnostic process allows for a more precise therapeutic approach. It not only confirms the diagnosis in cases of patients with a positive family history but also identifies asymptomatic mutation carriers among relatives, which enables early intervention. As already mentioned, specific genetic variants may indicate a more severe disease course and an increased risk of sudden cardiac death, which is significant for prognosis assessment and treatment personalization.

To complete the diagnostic instruments of HCM, we need to mention cardiac biomarkers like NT-proBNP (N-terminal pro-B-type natriuretic peptide) and hsTnI (high-sensitivity troponin I). They reflect the degree of cardiomyocyte stress and damage. In additional tests under consideration (though less commonly), galectin-3—a marker associated with myocardial fibrosis processes—and GDF-15 (growth differentiation factor-15), whose elevated levels correlate with the severity of inflammation in the course of the disease (Jansen et al., 2022).

Treatment

The main therapeutic goals are symptom reduction, improvement in quality of life, and prevention of cardiovascular incidents. Pharmacotherapy is the treatment of choice. Preferentially beta-blockers. Through sympathetic modulation, they reduce ventricular contractility, prolong the diastolic phase, and decrease the LVOTO gradient. Alternative paths include calcium channel blockers or disopyramide (Dybro et al., 2021).

Patients are also advised to control their weight, engage in moderate physical activity, maintain proper hydration, avoid alcohol, and avoid exposure to extreme temperatures as a part non-pharmacological treatment. Invasive methods of treatment are considered when pharmacotherapy is insufficient. In those cases surgical septal myectomy is the gold standard, but in elderly patients or those with significant comorbidities, percutaneous alcohol septal ablation (ASA) may be an alternative (Nishimura et al., 2017).

The progress in understanding the HCM's molecular mechanisms, along with the use of modern diagnostic methods (genetic and biomarker-based), opens the path to develop targeted, individualized therapies aligned to the clinical and genotypic characteristics of a specific patient (Abbas et al., 2024).

Mavacamten

Mavacamten (MYK-461) derives from the group of allosteric pyrimidine modulators - 6-[[(1S)-1-phenylethyl]amino]-3-propan-2-yl-1H-pyrimidine-2,4-dione. The drug selectively and reversibly inhibits cardiac myosin ATPase, which reduces the excessive contractile activity. It is the first targeted drug in the treatment of HCM (Zatorski et al., 2023). Under HCM pathophysiological conditions occurs increased ATP hydrolysis by myosin resulting in excessive actin-myosin interaction, impaired relaxation, and abnormal energy metabolism in cardiomyocytes. Mavacamten modulates this pathway. It reduces the number of available myosin heads capable of binding actin and lowers their mutual affinity. As a result, it decreases the generated contractile force of sarcomeres and normalizes the mechanical function of the heart muscle (Keam, 2022).

In clinical practice, mavacamten helps to reduce the LVOT pressure gradient and improve ventricular filling, which alleviates dyspnea and chest pain and increases exercise tolerance (Zatorski et al., 2023). Long-term mavacamten therapy may contain progressive heart remodeling - ventricular hypertrophy, microfilament destabilization, and myocardial fibrosis processes. Most importantly, it reduces the need for invasive treatment (Bishev et al., 2023).

Mavacamten is advised for patients with symptomatic obstructive HCM (patients who exhibit heart failure symptoms, NYHA class II-III) who have failed standard treatment (beta-adrenolytics or calcium channel blockers) fails to improve symptoms (Bishev et al., 2023). Mavacamten can potentially worsen myocardial contractile function; therefore, the drug is not advised in patients with a left ventricular ejection fraction (LVEF) beyond 55% (Keam, 2022).

Women of reproductive age should use effective contraception therapy and for 4 months after treatment ends due to teratogenicity revealed in preclinical trials. Potential impact on breastfed infants remains unknown, since there is not enough data on the drug's passage into breast milk. Patients with concurrent liver dysfunction also require attention. The safety and efficacy of mavacamten in severe liver failure have not been established. Mild or moderate liver impairment can possibly lead to a significant increase in drug exposure (Bello and Pellegrini, 2024). Among the most frequently reported adverse effects associated with the use of mavacamten are transient episodes of atrial fibrillation and reduced LVEF. Regular cardiac function monitoring during therapy is advised (Bishev et al., 2023).

EXPLORER-HCM trial was a randomized, double-blind, placebo-controlled phase III trial that consisted of 251 patients with symptomatic oHCM and NYHA class II or III heart failure symptoms with an LVOT gradient ≥50 mmHg at rest or after provocation. The primary endpoint of the study was a composite assessment of improvement which was noted as achieved if a patient experienced an increase in peak oxygen uptake (peak VO_2) of at least 1.5 mL/kg/min and a reduction in NYHA class by at least one grade. (Olivotto et al., 2020).

There was a distinct difference between patients who received mavacamten and achieved the composite endpoint compared to placebo group (37% vs. 17%). Another observation was a statistically significant reduction in LVOT gradient (mean intergroup difference: 20 mmHg - 36 mmHg in the active group vs. 16 mmHg in placebo). Additionally, analysis of secondary endpoints (e.g., the KCCQ questionnaire) revealed clinically meaningful improvement in quality of life and physical function parameters (Ho et al., 2020a; Olivotto et al., 2020).

In the next phase of clinical research, the randomized phase III VALOR-HCM trial was conducted to evaluate the efficacy of mavacamten in reducing the need for invasive therapeutic methods in oHCM patients. The study enrolled patients scheduled for planned ASA or surgical myectomy. The trial lasted 16 weeks. Participants received mavacamten or placebo in a double-blind trial. The aim was to measure the number of patients still qualifying for SRT after completing the study period.

The results showed that only 18% of patients still met the criteria for SRT (compared to 77% in the placebo group), which confirms that mavacamten significantly reduces the need for invasive interventions. Additionally, researchers observed a significant reduction in LVOT gradient, increased exercise tolerance, and alleviation of heart failure symptoms among patients taking mavacamten. This allows one to believe in a potential change in advanced HCM's therapeutic standards (Desai et al., 2023).

The aim of the MAVERICK-HCM trial was to assess the safety and tolerability of mavacamten in patients with non-obstructive HCM. It was a phase II study that consisted of 69 patients. The researchers analyzed the drug's impact on selected biomarkers of myocardial stress, like NT-proBNP and cardiac troponin. The study results established the drug's acceptable safety profile and that treatment was well-tolerated by patients. The active group exhibited a significant reduction in cardiac biomarkers. That indicates reduced myocardial strain. Although the study was not designed to assess hard endpoints, the observed changes in selected biomarkers allow us to suspect potential efficacy in non-obstructive HCM patients. However, further clinical trials are necessary to verify these preliminary observations and establish optimal indications for use in this patient population (Ho et al., 2020b).

The purpose of the MAVA-LTE (Long-Term Extension) trial is to monitor patients who have participated in previous clinical studies of mavacamten to evaluate the durability of the drug's therapeutic effects and the drug's long-term safety. Initial analyses showed that the clinical benefits of mavacamten persist over time with a maintained safety profile and without new significant adverse effects. The obtained knowledge is particularly important in the context of the chronic nature of HCM therapy requiring long-term and stable treatment (Rader et al., 2024).

This study is dedicated to HCM – the most common genetically determined myocardial disorder. HCM's primary cause lies in mutations in genes encoding sarcomeric proteins. Understanding of molecular basis of HCM pathogenesis as well as correlations between genotype and phenotype, are the key to the development of targeted therapeutic methods (Maron et al., 2006).

HCM diagnosis and treatment have progressed significantly over the last decade. Introduction of targeted molecular therapies capable of selectively influencing specific signaling pathways in cardiomyocytes presented new therapeutic possibilities. The article is an overview of the pathophysiological mechanisms of HCM and the most recent progress in diagnosis and treatment, with particular emphasis on the role of Mavacamten – a selective, allosteric inhibitor of cardiac myosin – as a breakthrough in therapeutic approach (Table 1).

Table 1. Summary of mavacamten's development.

Effects	• significant reduction in LVOT gradient, • improved quality of life
Clinical benefit:	Significant reduction of invasive interventions with mavacamten treatment.
Challenges:	• Lack of data for the group of patients with LVEF >55%. • Potential for LV function suppression and arrhythmia. • Requires regular monitoring (ECHO, EKG). • High cost of therapy.

4. CONCLUSION

HCM is rooted in genetic mutations that lead to a disease of the heart muscle, which is heterogeneous both clinically and genetically. Modern imaging techniques and genetic testing have enabled the identification of patients at risk of an unfavorable course of the disease. Thanks to the multimodal approach we can diagnose HCM more accurately and try to personalize treatment. The clinical trials demonstrated the drug's efficacy in reducing LVOT gradient and improving quality of life, while long-term data confirm the durability of effects and a favorable safety profile.

Despite the progress, challenges remain – we still lack data on mavacamten's effect on non-obstructive HCM and need further research on the impact of treatment on prognosis and mortality. The combined approach of genetic diagnostics with targeted therapy opens prospects for personalized treatment but still requires further development.

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Author's contribution

Małgorzata Bacik: Conceptualization, writing - rough preparation, investigation
Klaudia Głodowska: Methodology, project administration
Kinga Piela: Formal analysis, supervision
Kacper Kiereta: Visualization, data curation
Zuzanna Cichowska: Conceptualization, data curation
Jakub Żelazo: Conceptualization, methodology
Katarzyna Wacławek: Resources, writing - rough preparation
Aleksandra Rechcińska: Conceptualization, writing - rough preparation
Anna Ciesielka: Resources, data curation
Bartłomiej Józef Rdzanek: Resources, investigation

Laura Chmielowiec: Writing - Review and editing, supervision
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Conflict of interest
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Data and materials availability
All data associated with this work are present in the paper.

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