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# PDA Closure in the Presence of a Dilated Main Pulmonary Artery and Ductal Spasm: Importance of Proper Technique and Hardware Selection

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## Abstract

Transcatheter Patent Ductus Arteriosus (PDA) closure is a device-based technique for correcting PDA. In general, an isolated PDA is easier to close, but conditions such as a smaller PDA, PDA spasm, or a dilated main pulmonary trunk make device closure a significant challenge. Moreover, re-crossing the PDA becomes difficult in situations if there is device size mismatch. This article highlights the management of PDA device closure in a patient with a smaller PDA and a dilated main pulmonary artery due to severe pulmonary stenosis, complicated by ductal spasm. It also emphasizes the importance of selecting the proper hardware to address this situation effectively.

## Keywords

Patent ductus arteriosus, device closure of PDA, dilated MPA, severe PS, Ductal Spasm.

## Introduction

The ductus arteriosus is a central vascular shunt connecting the proximal descending aorta to the pulmonary artery near the origin of the left branch of the pulmonary artery.[1] It allows oxygenated blood from the placenta to bypass the uninflated fetal lungs and enter the systemic circulation. Rapid closure of the ductus arteriosus after birth is essential for the vascular transition to a mature, divided pattern of arteriovenous circulation.[1,2] As the clinical signs and symptoms of PDA can vary, all patients at risk of developing or having PDA should undergo echocardiography.[6] Closure is recommended for patients regardless of the presence or absence of symptoms. Transcatheter device closure is the treatment of choice for all patients whenever it is technically feasible.[1-5] Ductal spasm is common in smaller PDAs, and utmost care should be taken to avoid undersizing the device. Ductal spasm during the procedure can lead to procedural failure.[2,7]

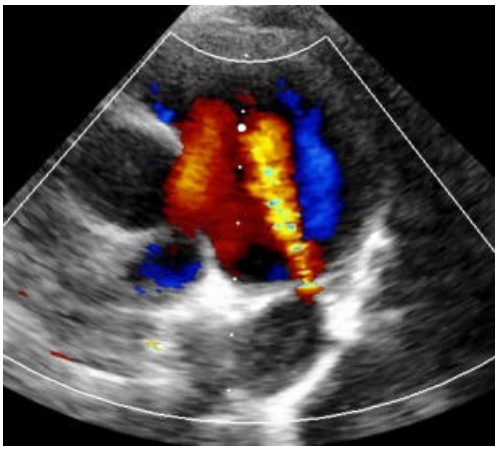

**FIGURE 1** *Transthoracic echocardiogram showing PDA with left-to-right shunt.*

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## Case Report

A seven-year-old male child, born to a diabetic mother from a non-consanguineous marriage, presented with a history of respiratory distress immediately after birth, for which he received NICU care during the neonatal period. The patient never underwent a screening echocardiogram during infancy. During a consultation for exertional breathlessness while playing, he was evaluated and underwent screening echocardiography. The echocardiogram (**Figure 1**) suggested a small 2 mm PDA with a left-to-right shunt, moderate pulmonary valve stenosis with a peak gradient of 48 mmHg, and a dilated main pulmonary artery measuring 34 mm.

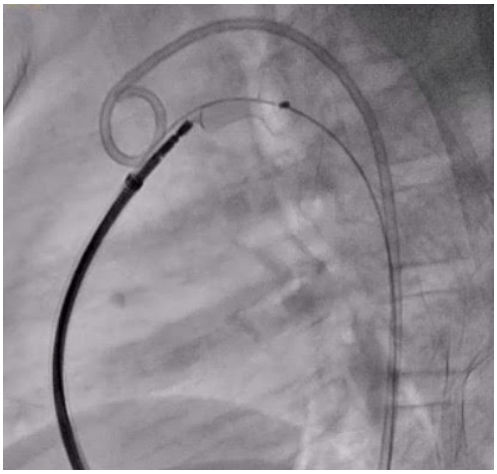

**FIGURE 2** *Fluoroscopic image showing PDA device expanded across the PDA with the Terumo wire maintained across the defect.*

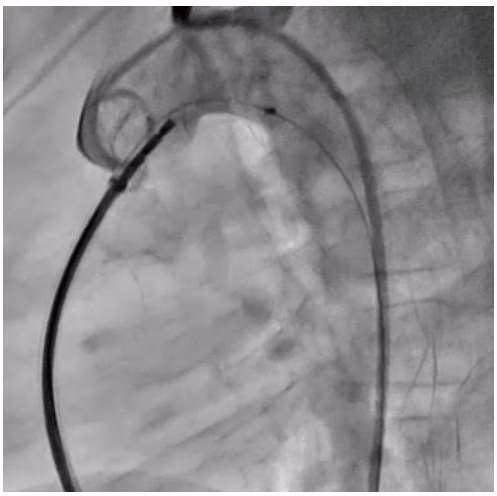

**FIGURE 3** *Fluoroscopic image showing the inflated PDA device in situ with no residual shunt across the defect.*

## Procedure

Procedure was done under general anesthesia. Right femoral artery and vein, along with left femoral venous access, were established and 6F sheaths were inserted. A 6F pigtail catheter was advanced through the right femoral artery along the descending aorta up to the PDA defect. An aortic angiogram was performed via the pigtail catheter to visualize and confirm the size of the defect. Pressures across the main pulmonary artery (MPA) were recorded using a 6F MPA catheter. A 0.025 mm J-tip Terumo wire was passed through the right femoral vein into the right atrium, followed by the right ventricle, and then into the main pulmonary artery. The MPA catheter was replaced with a 6F Judkins right catheter. Due to the dilated MPA and PDA spasm from repeated attempts to cross the defect, there was difficulty in advancing the terumo wire through the defect. After multiple attempts, the 0.025 mm Terumo wire was successfully passed through the defect and subsequently exchanged for an Amplatzer Super Stiff wire. The ductal spasm led to a possible underestimation of the required device size. A Lifetech CERA 8/6 mm device was loaded onto the device delivery sheath. To facilitate the challenging recrossing, a Mullins long sheath, one size larger than recommended for the Lifetech CERA device, was inserted and advanced up to the defect over the Amplatzer Super Stiff wire. The Super Stiff wire was then exchanged for the Terumo wire, which was snared through the left femoral artery to secure access during the trial of device placement (**Figure 2**). The device was then passed through the defect, and both the aortic and MPA ends of the device were sequentially expanded. A check aortic angiogram showed no residual shunt across the device (**Figure 3**). The Terumo wire was then gently removed, and the device was released in place (**Figure 4 & 5**).

## Post Procedure

Postoperative transthoracic echocardiography confirmed the correct device position with no residual shunt across the device (**Figure 6**). Patient recovery after procedure was uneventful. Patient was planned for BPV after one year of follow up and was discharged thereafter.

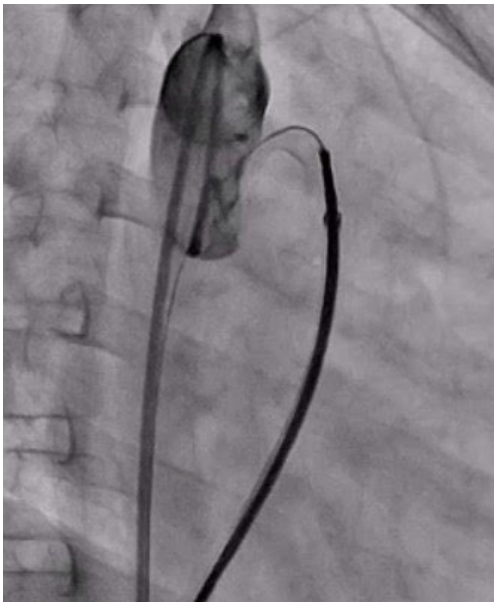

**FIGURE 4** *Fluoroscopic image showing the expanded PDA device in situ with no residual shunt across the defect.*

## Discussion

PDA is a common congenital heart disease (CHD) having a broad spectrum of clinical manifestation, varying from asymptomatic cardiac murmur to heart failure. PDA comprises 5 – 10 % of all CHDs. PDA is most commonly seen in females than males.[1,2] In advance cases, PDA, if not treated, can cause heart failure and Eisenmenger syndrome.[1] Many studies have shown transcatheter device closure of PDA is superior to surgical closure as it is safe with high success rate and little morbidity when compared with surgical closure.[1-4,7] Moreover, surgical closure of PDA is associated with complications like pneumothorax, bleeding and recurrent laryngeal nerve injury.[4] Surgical closure in adults can be challenging secondary to calcified ductus, left ventricular dysfunction, and pulmonary artery hypertension.[4] Nowadays, surgical closure of PDA is restricted to cases with larger PDA, unsuitable anatomy like aneurysmal PDA.[4] Ductal Spasm occurs during repeated manipulation of wire is a well-known complication which can sometimes lead to procedural failure. Absence of

murmur can confirm the diagnosis of ductal spasm.[2] PDA is considered to be small when it is < 1.5 mm, moderate when it ranges from 1.5 and 3 mm and large if its dimension is more than 3 mm.[6] If pulmonary vascular resistance is elevated, a large PDA may not exhibit significant left-to-right shunting. Instead, the presence of a right-to-left shunt suggests considerable pulmonary hypertension. In such cases, closing the ductus abruptly is not recommended, as it may lead to worsening right heart failure.[3] For larger defects, ADO I device is preferred over ADO II, which is preferred for small-to-medium sized defects. Transcatheter device closure is considered superior to coils.[4,5] When closing a PDA via catheter-based intervention, two primary approaches are used: antegrade and retrograde. Antegrade approach is through venous route and the catheter is advanced from right atrium to right ventricle to pulmonary artery and crossing PDA and getting into descending aorta. In this approach, the device is delivered from the aortic side. Retrograde approach is where the catheter is advanced from arterial system inside descending aorta followed by crossing PDA and getting to pulmonary side. In this approach, the device is delivered from the aortic side.[4,7] Snaring of guidewire is typically done in an antegrade approach, as the sheath is inserted through pulmonary side and it may be difficult to position delivery sheath correctly. Snaring can also help to facilitate a smooth device, better stability, and better control during crossing of device through PDA.[4,7] Snaring of the guidewire is useful in cases with smaller PDA, dilated MPA and in cases requiring more controlled and stable delivery system manipulation.[2,4]

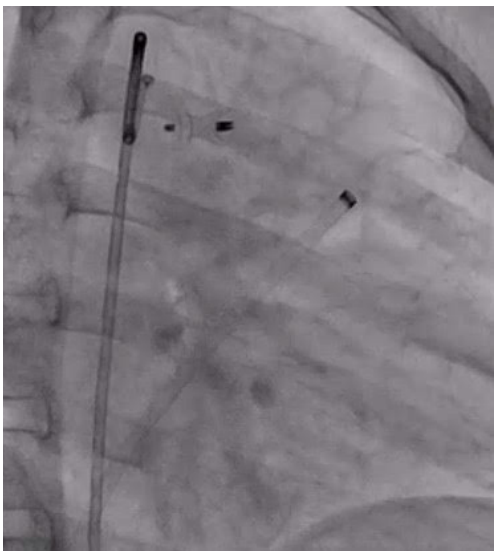

**FIGURE 5** *Final fluoroscopic image showing PDA device in place after release.*

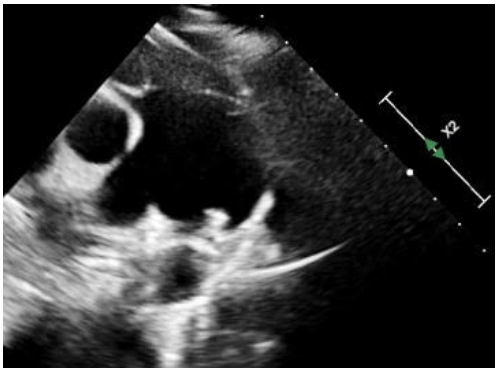

**FIGURE 6** *Post-procedure 2D echocardiography showing the PDA device in place.*

Challenges faced during closure of PDA in our case were:

1. *Dilated MPA:* The dilated MPA did not provide sufficient support to our catheter for advancing the Terumo wire through the lesion, leading to repeated attempts to cross the defect.
2. *Ductal Spasm:* The need of repeated manipulation to cross PDA resulted in ductal spasm.
3. *Underestimation of Device Size:* The ductal spasm presented a risk of underestimating the device size required for closure.
4. *Larger Mullins Long Sheath:* A larger-sized Mullins long sheath was selected to ensure incorporation of both device and double length terumo wire simultaneously.
5. *Wire and Device Positioning:* The Terumo wire was reinstated prior to device positioning and snared across the defect to ensure access, even in the event of device size mismatch or failure to plug the device.

Hence, in this case we preferred: an antegrade approach to deal with situation, a larger-size delivery system was used to incorporate both terumo wire and device into it, snaring of guidewire before positioning device over the defect to prevent recrossing of wire in this challenging condition and removing guidewire before final placement of device across PDA.

## Conclusion

Closing a PDA through catheter-based methods can be more challenging when dealing with a small PDA, a dilated main pulmonary artery and complications like ductal spasm. In such complex cases, careful planning is essential. This includes a detailed assessment of the PDA size and shape, as well as choosing the right devices and techniques tailored to the patient's specific anatomy. Being aware of potential issues, such as ductal spasm, and being prepared to adjust strategies as needed are crucial for a safe and effective PDA closure.

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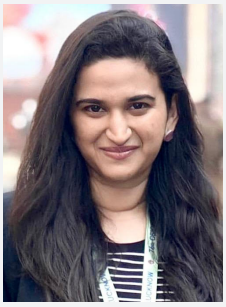

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# Tenaya Therapeutics Publishes Preclinical Data Demonstrating TN-201 Enhances Cardiac Function and Survival in MYBPC3 Cardiomyopathy Models

*Robust Evidence of Disease Reversal in Severe Knock-Out Mice Model Supports Tenaya's Clinical Development Plan to Evaluate TN-201 as a Potential Treatment for Patients with MYBPC3-associated Hypertrophic Cardiomyopathy*

Tenaya Therapeutics, Inc. (Nasdaq: TNYA), a clinical-stage biotechnology company with a mission to discover, develop and deliver potentially curative therapies that address the underlying causes of heart disease, today announced the publications of positive preclinical data for TN-201, the company's gene therapy candidate for Myosin-Binding Protein C3 (MYBPC3)-associated hypertrophic cardiomyopathy (HCM), in Nature Communications.

Variants in the MYBPC3 gene resulting in insufficient levels of MyBP-C protein are the most common genetic cause of HCM. TN-201 is Tenaya's adeno-associated virus serotype 9 (AAV9)-based gene therapy designed to deliver a working MYBPC3 gene to heart muscle cells via a single intravenous infusion, increasing MyBP-C protein levels to address the underlying cause of MYBPC3-associated HCM with the aim of halting or even reversing disease. Preclinical results published in Nature Communications show that Tenaya's MYBPC3 gene replacement therapy achieved dose-dependent increases in MyBP-C protein, improving multiple parameters of cardiac function at protein levels well below wild-type with doses as low as 1x1013 vg/kg. Of note, treatment with Tenaya's MYBPC3 gene therapy reversed left ventricular hypertrophy, a hallmark of HCM, as evidenced by decreases in posterior wall thickness relative to vehicle and normalization of left ventricular mass relative to body weight. TN-201 is currently being evaluated at doses of 3x1013 vg/kg and 6x1013 vg/kg in Tenaya's ongoing MyPEAK™-1 Phase 1b/2 clinical trial for the treatment of MYBPC3-associated HCM.

"The extensive body of preclinical data published in Nature Communications highlights the engineering, production and thorough testing that support TN-201's clinical development and offers substantial evidence that our novel gene therapy approach to MYBPC3-associated HCM has the potential to change the treatment paradigm for patients suffering with this genetic heart condition," said Kathy Ivey, Ph.D., Senior Vice President of Research of Tenaya Therapeutics.

"We are encouraged by TN-201's consistency in achieving transduction and expression across our preclinical studies and the early findings from our first-in-human Phase 1b study of TN-201," added Whit Tingley, M.D., Ph.D., Tenaya's Chief Medical Officer. "The robust transduction and improvements in cardiac function observed in a model of severe disease, provide reason to believe in TN-201's potential to achieve similar improvements in key parameters of human disease over time. We look forward to presenting additional data from our first cohort of patients in the MyPEAK-1 clinical trial at the upcoming American College of Cardiology Scientific Sessions, as well as sharing initial data from our high-dose cohort in the second half of this year."

## Key Preclinical Findings

The article, titled, "AAV9-Mediated MYBPC3 Gene Therapy with Optimized Expression Cassette Enhances Cardiac Function and Survival in MYBPC3 Cardiomyopathy Models," describes the results from in vitro and in vivo preclinical studies.

Studies conducted in human-induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) compared various cassette configurations and informed the final design of TN-201, which incorporates a full-length MYBPC3 gene with a proprietary cardiac promoter that maintains high specificity for heart cells.

To test transduction and expression strength, additional analyses in human iPSC-derived cardiomyocytes showed transduction equivalent to one vector genome per diploid genome (vg/dg) resulted in near-wild type levels of MYBPC3 RNA and MyBP-C protein at 3x1013 vg/kg. Researchers observed proportional increases in transgene RNA at doses of 3x1013 and 1x1014 vg/kg, while MyBP-C protein levels did not exceed wild type levels, indicating that RNA overexpression does not result in overexpression of protein, suggesting an attractive safety feature of MYBPC3 gene therapy.

To measure the efficacy of TN-201, a mouse surrogate of TN-201 (mTN-201) was tested against vehicle in a homozygous Mybpc3-deficient murine model that mimics severe disease in humans. Treatment with mTN-201 in Mybpc3 knock-out mice at the time of disease onset or in a more challenging model of advanced disease resulted in:

- Sustained increases in Mybpc3 RNA and MYBPC3 protein expression
- Decreased cardiac biomarkers associated with fibrosis and heart failure
- Improved cardiac function, including improved ejection fraction and diastolic function
- Heart remodeling
- Extended survival

These results were dose dependent, with near-maximal efficacy achieved at doses of 3x1013 vg/kg, and durable, lasting out to 20 months post-treatment.

Additional experiments in human engineered heart tissue models that replicate the hypercontractility associated with MYBPC3-associated HCM demonstrated:

- Resolution of calcium-handling abnormalities
- Enhanced diastolic activity

The complete article can be accessed at Nature Communications and within the Publications and Presentations section of Tenaya Therapeutics' website.

## About MYBPC3-Associated Hypertrophic Cardiomyopathy

Variants in the MYBPC3 gene are the most common genetic cause of hypertrophic cardiomyopathy (HCM), accounting for approximately 20% of the overall HCM population, or 120,000 patients, in the United States alone.[1] MYBPC3-associated HCM is a severe and progressive condition affecting adults, teens, children and infants. Mutations of the MYBPC3 gene result in insufficient expression of a protein, called MyBP-C, needed to regulate heart contraction. The heart becomes hypercontractile and the left ventricle thickens, resulting in symptoms such as chest pain, shortness of breath, palpitations and fainting. Patients whose disease is caused by MYBPC3 mutations are more likely than those with non-genetic forms of HCM to experience earlier disease onset and have high rates of serious outcomes, including heart failure symptoms, arrhythmias, stroke and sudden cardiac arrest or death.[2] There are currently no approved therapeutics that address the underlying genetic cause of HCM.

## About the MyPEAK-1 Phase 1b/2 Clinical Trial

The MyPEAK-1 Phase 1b/2 clinical trial (Clinicaltrials.gov ID: NCT05836259) is an ongoing, multi-center, open-label, dose-escalating study designed to assess the safety, tolerability and clinical efficacy of a one-time intravenous infusion of TN-201 gene replacement therapy. The trial is enrolling symptomatic (New York Heart Association Class II or III) adults who have been diagnosed with MYBPC3-associated HCM. MyPEAK-1 is testing doses of 3E13 vg/kg and 6E13 vg/kg in two cohorts of three patients each. MyPEAK-1 may enroll up to 24 MYBPC3-associated HCM adults with either nonobstructive or obstructive forms of HCM in planned dose expansion cohorts.

To learn more about gene therapy for HCM and participation in the MyPEAK-1 study, please visit **HCMStudies.com**.

## About Tenaya Therapeutics

Tenaya Therapeutics is a clinical-stage biotechnology company committed to a bold mission: to discover, develop and deliver potentially curative therapies that address the underlying drivers of heart disease. Tenaya employs a suite of integrated internal capabilities, including modality agnostic target validation, capsid engineering and manufacturing, to generate a portfolio of genetic medicines aimed at the treatment of both rare genetic disorders and more prevalent heart conditions. Tenaya's pipeline includes TN-201, a gene therapy for MYBPC3-associated hypertrophic cardiomyopathy (HCM), TN-401, a gene therapy for PKP2-associated arrhythmogenic right ventricular cardiomyopathy (ARVC), TN-301, a small molecule HDAC6 inhibitor intended for heart failure with preserved ejection fraction (HFpEF), and multiple early-stage programs in preclinical development.

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## Forward-Looking Statements

This press release contains forward-looking statements as that term is defined in Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. Statements in this press release that are not purely historical are forward-looking statements. Words such as "potential," "believe," "look forward," and similar expressions are intended to identify forward-looking statements. Such forward-looking statements include, among other things, the clinical, therapeutic and commercial potential of, and expectations regarding TN-201; the value of preclinical data to inform the potential of TN-201; the planned timing to report additional data from MyPEAK-1; statements regarding the continued development of TN-201; and statements made by Tenaya's Senior Vice President of Research and Chief Medical Officer. The forward-looking statements contained herein are based upon Tenaya's current expectations and involve assumptions that may never materialize or may prove to be incorrect. These forward-looking statements are neither promises nor guarantees and are subject to a variety of risks and uncertainties, including but not limited to: the potential failure of TN-201 to demonstrate safety and/or efficacy in clinical testing; the potential for any MyPEAK-1 clinical trial results to differ from preclinical, interim, preliminary or expected results; availability of MyPEAK-1 data at the referenced times; the timing and progress of MyPEAK-1; Tenaya's ability to enroll and maintain patients in clinical trials, including MyPEAK-1; risks associated with the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics and operating as an early stage company; Tenaya's continuing compliance with applicable legal and regulatory requirements; Tenaya's ability to raise any additional funding it will need to continue to pursue its product development plans; Tenaya's reliance on third parties; Tenaya's manufacturing, commercialization and marketing capabilities and strategy; the loss of key scientific or management personnel; competition in the industry in which Tenaya operates; Tenaya's ability to obtain and maintain intellectual property protection for its product candidates; general economic and market conditions; and other risks. Information regarding the foregoing and additional risks may be found in the section titled "Risk Factors" in Tenaya's Annual Report on Form 10-K for the year ended December 31, 2024, and other documents that Tenaya files from time to time with the Securities and Exchange Commission. These forward-looking statements are made as of the date of this press release, and Tenaya assumes no obligation to update or revise any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

# SCAI Publishes Expert Consensus on Alternative Access for Transaortic Valve Replacement (TAVR)

The Society for Cardiovascular Angiography & Interventions (SCAI) has published an expert consensus statement that provides interventional cardiologists, cardiothoracic surgeons, and heart teams with practical guidance for selecting patients and performing alternative access transaortic valve replacement (TAVR).

TAVR has seen substantial growth over the past decade, becoming a standard of care for many patients with asymptomatic aortic stenosis. However, some patients face challenges due to inadequate femoral vascular access. The new guidelines address this gap by recommending alternative access techniques that are safer and more effective.

"While devices have improved, there remains a need for robust techniques to provide TAVR to patients without adequate femoral access. Our guidelines focus on the safest and most effective alternative access methods based on observational evidence," said Matthew W. Sherwood, MD, MHS, FSCAI, Co-Chair of SCAI's Structural Heart Disease Council and System Director of Interventional Cardiology at Inova Schar Heart and Vascular Institute. "The guidelines are particularly beneficial for older, sicker patients with significant vascular disease. These high-risk patients often face complications during TAVR procedures. By standardizing alternative access techniques, we aim to improve outcomes and expand treatment options for these patients."

Published in JSCAI, "SCAI Expert Consensus Statement on Alternative Access for Transcatheter Aortic Valve Replacement" highlights two preferred alternative access techniques: transcarotid and transcaval access. These methods are favored over others, such as transaxillary access, due to their lower associated stroke risk and better overall outcomes. The guidelines discourage the use of older techniques like transapical or direct aortic access. The document also highlights the advancements in device technology and imaging guidance that have contributed to improving the safety and efficacy of alternative access TAVR.

"With this expert consensus document, we aim to help clinicians better care for their patients by providing guidance on the safest and most efficacious routes for alternative access to TAVR. This is crucial as the TAVR population continues to grow," said Paul D. Mahoney, MD, FSCAI, a member of the SCAI Structural Heat Disease Council and Section Chief, Interventional Cardiology and Director of Structural Heart Programs, East Carolina University Brody School of Medicine. "TAVR as a field is maturing from a novel procedure to a standard of care. The goal is to help busy clinicians identify best clinical practices and achieve the best outcomes for their patients."

The guidelines call for better standardization and focus on alternative access techniques at individual sites, such as the use of proctors to gain expertise. The guidelines emphasize the need for further research and standardization, as more data is needed to fully understand the risks and benefits of TAVR alternative access techniques. The guidelines also call for the exploration of newer techniques, such as intravascular lithotripsy, to further improve patient outcomes.

"There is still a lot we don't know, and we want to ensure that we provide the best care for our patients by continuing to study and improve these techniques," Dr. Sherwood said.

Read the full statement here:
https://www.jscai.org/article/S2772-9303(24)02203-8/fulltext

# Congenital Heart Defects May Be Linked to Increased Cancer Risk in Babies and Mothers

Being born with a heart defect may be associated with an increased cancer risk for babies and their moms, according to new research published today in the American Heart Association's flagship journal Circulation.

According to the American Heart Association, the most common birth defects in the U.S. are forms of Congenital Heart Defects (CHD). They range from structural abnormalities, such as openings between the heart's chambers, to severe malformations, such as the absence of heart chambers or valves. In the US, about 12 infants in 1,000 births have a Congenital Heart Defect, according to the Association's 2025 Heart Disease and Stroke Statistics. While numerous medical advances have enabled children with heart defects to survive longer than they used to, some research suggests they may be at higher risk for developing other conditions including cancer.

Researchers analyzed health information about more than 3.5 million live births from the Korean National Health Insurance Service database from 2005 to 2019. They followed all newborns and mothers for cancer diagnoses for an average of 10 years.

The findings show that care for congenital heart defects may benefit from including different health care professionals to provide well-rounded care for families, he said.

The analysis found:

- Overall, the incidence of cancer was 66% higher in newborns with congenital heart defects compared to those born without a heart defect.
- Specifically, compared to newborns without congenital heart defects, cancer risk was more than double in newborns with congenital defects that involved blood vessels or heart valves and two times higher among those with complex congenital heart disease.
- The most common types of cancers that developed among all of the children, both with and without congenital heart defects, were leukemia (21%) and Non-Hodgkin lymphoma (11%).
- Mothers who gave birth to newborns with congenital heart defects were 17% more likely to be diagnosed with cancer in the 10-year follow-up period compared to mothers who gave birth to newborns without a congenital heart defect.

Researchers have yet to determine why having a baby with a congenital heart defect is associated with a higher risk for cancer in mothers. Potential factors include the mother's genetic predisposition or a mutation known to contribute to cancer and congenital heart defect risks in newborns.

"The genetic variants inherited from the mother may provide the necessary environment for cancer to develop in Congenital Heart Defect patients, highlighting a possible shared genetic pathway underlying both conditions," Huh said.

American Heart Association volunteer expert Keila N. Lopez, MD, MPH, said the study's finding of a cancer association among mothers of infants with congenital heart defects was surprising.

"This finding needs to be further explored to understand if there are environmental factors affecting genes (epigenetics) or stress-related changes linking congenital heart defects with maternal cancer risk," said Lopez, chair of the Association's Young Hearts Congenital Cardiac Defects Committee and an associate professor of pediatric cardiology at Texas Children's Hospital, Baylor College of Medicine in Houston. "There is some data that suggests stress is related to cancer risk, and having a child with a congenital heart defect can be very stressful. So having studies that investigate and demonstrate all the links between cancer and congenital heart defects will help us understand lifelong risks of not only heart defects but also the development of cancer within families."

The study also emphasizes the importance of follow-up care with a pediatric cardiologist and primary care physicians and the need for lifelong care for ongoing surveillance of those born with congenital heart defects, Lopez said.

Study limitations include the possibility that unknown factors may have biased study results, and some analyses lacked power due to a small number of specific types of congenital heart defects. While the study was from data for people in Korea, Huh said the findings may apply to other populations.

Study details, background and design:

- Researchers reviewed health information for more than 3.5 million babies in Korea born with and without congenital heart disease (51.5% boys, 48.5% girls). Of the live births, 72,205 newborns had a congenital heart defect. Mothers (19,310) who had a history of cancer were excluded from the analysis.
- The analysis of the nationwide study was conducted using data from the Korean National Health Insurance Service database from January 1, 2005, to December 31, 2019. Called K-NHIS data, the information included individual-level demographics, and all records of diagnosis and health care (including office visits, prescriptions and medical procedures), as well as provided inpatient, outpatient and emergency department visits.
- For a cancer diagnosis to be counted in this study, the same International Classification of Diseases 10th Revision (ICD-10) cancer code had to appear at least three times within a year in the medical records or result in at least one inpatient hospitalization.
- The analysis was performed in 2024.

# Scientists Uncover Hidden Genetic Causes of Congenital Heart Disease

Scientists at the Icahn School of Medicine at Mount Sinai and collaborators have identified novel genetic interactions that may contribute to Congenital Heart Disease (CHD), a common birth defect. Details on their findings were reported in the February 20 online issue of The American Journal of Human Genetics [DOI: 10.1016/j.ajhg.2025.01.024].

"Our research reveals the potential for digenic inheritance-where two genes work together to cause disease - expanding our understanding of the genetic underpinnings of Congenital Heart Disease," says co-corresponding senior author Yuval Itan, PhD, Associate Professor of Genetics and Genomic Sciences, a core member of The Charles Bronfman Institute for Personalized Medicine, and a member of The Mindich Child Health and Development Institute at the Icahn School of Medicine at Mount Sinai. He co-supervised the study with Bruce Gelb, MD, Gogel Family Professor and Director of The Mindich Institute. "By identifying these gene pairs and their combined effects, we uncover previously hidden genetic risks, which could improve diagnostic precision and open new avenues for personalized treatment strategies."

Congenital Heart Disease is the most common congenital anomaly, affecting millions worldwide. Despite decades of research, more than half of CHD cases still lack a molecular diagnosis. By analyzing trio exome sequencing data from affected and unaffected children in the Pediatric Genomic Consortium (PCGC), the team identified 10 novel gene pairs potentially linked to the development of CHD.

The research team used a robust computational method to identify gene pairs that may act together to cause CHD. This innovative approach could transform how genetic studies are conducted for complex diseases, providing deeper insights into the role of genetics in disease development, say the investigators.

The study also paves the way for advancing genetic diagnoses in other complex disorders. "With the tools we've developed, our research provides a framework for future studies into genetic interactions that could affect a wide range of human diseases," says Dr. Itan.

Next, the researchers plan to apply the digenic approach to other disease groups that have traditionally been studied using the monogenic model, potentially explaining some of the missing heritability in these disorders. Ultimately, they aim to extend the digenic approach into a robust polygenic framework capable of identifying multiple disease-causing variants and genes in patients.

"Our findings hold promise for improving genetic diagnoses, offering better risk assessments, and ultimately guiding more personalized treatments for individuals with congenital heart disease," says Dr. Kars.

The paper is titled "Deciphering the digenic architecture of congenital heart disease using trio exome sequencing data."

The remaining authors are David Stein (PhD student at the Icahn School of Medicine at Mount Sinai); Peter D. Stenson, (Cardiff University, UK); David N. Cooper, PhD (Cardiff University, UK); Wendy K. Chung, MD, PhD (Boston Children's Hospital and Harvard Medical School); Peter J. Gruber, MD, PhD (Yale School of Medicine); Christine E. Seidman, MD, (Harvard Medical School, Brigham and Women's Hospital, Howard Hughes Medical Institute); Yufeng Shen, PhD (Columbia University Irving Medical Center); and Martin Tristani-Firouzi, MD (University of Utah School of Medicine).

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# MAY

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