



The Beat

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Patient Perspective: Mark Scagliarini's Story

Mark is an avid cyclist and businessman who experienced a blood clot in his leg in August of 2017, while training and competing in the Pan-Mass Challenge. After his blood clot, Mark was uncertain about what had caused the blood clot and stopped cycling all together, fearing that exercise could make his condition worse. Frustrated and looking for answers, Mark found NATF's Boston-based support group.



Q: When did you realize you had a blood clot?

I was diagnosed in August 2017.

I had just completed the Pan-Mass Challenge (a 190 mile "bike-a-thon" that raises money for cancer research at Dana-Farber Cancer Institute) in August of last year when I was diagnosed.

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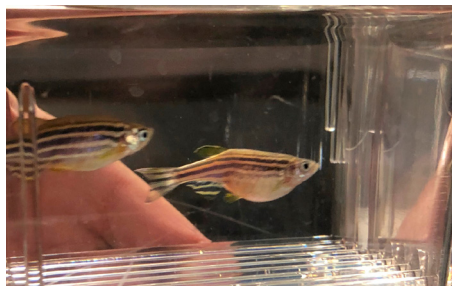
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Zebrafish: A Surprising Partner in the Fight Against Blood Clots

Who would have thought that a tiny fish could change how healthcare providers study human health?

Meet the zebrafish.

This small fish serves as an important tool in scientific research. Believe it or not, it has become a big player in the fight against blood clots.



A pregnant zebrafish



WHAT ARE ZEBRAFISH?

Zebrafish are small freshwater fish that belong to the minnow family. These important little fish originate from the Himalayan region, but can be found in household aquariums across the United States.

Zebrafish were first used in scientific research in the 1970s. Today, they are used in laboratories to research a wide range of topics because they can be used to model biological systems, such as the human body. Their genome, or complete set of genetic material, has been fully sequenced and is well understood. They also reproduce quickly, allowing for multiple generations to be observed in a short time span.

At Brigham and Women's Hospital in Boston, these fish play an important role in groundbreaking research. They are used in research done by oncologists, developmental biologists, cardiologists, and more.

"We have hundreds, maybe thousands, of tanks here and each tank can hold 15-20 fish," said Dr.

Aaron Kithcart, explaining the capacity of Brigham and Women's zebrafish lab. Dr. Kithcart is a vascular medicine fellow who carries out research with these fish at Brigham and Women's Hospital. "We have tens of thousands of adult zebrafish."



Tanks of zebrafish at Brigham and Women's Hospital

Dr. Kithcart uses the zebrafish to study cardiovascular health and acknowledges that it may surprise people to learn that a small fish can be used to carry out research related to the human body.

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Upcoming Events

In-Person Blood Clot Support Group at BWH

June 26, 2018

There will be no in-person support group for July and August. We look forward to seeing you all in the fall!

All support groups start at 7:00 p.m. and are held at Brigham and Women's Hospital. To register, email Kathryn Mikkelsen at KMikkelsen@NATFonline.org or call 617-730-4120.

Online Blood Clot Support Group

June 5 with Lynn Oertel, NP – Keeping Up with The Clots: The Importance of Medication Adherence

July 10 with Dr. Gregory Piazza – Back to the Basics: What are blood clots and how do they form?

August – Summer Vacation

NATF's Online Blood Clot Support Group offers patients the opportunity to share common concerns, offer support to one-another, and learn up-to-date and accurate information, including new research on blood clot prevention and treatments. Dates and speakers for our upcoming meetings can be found at www.natfonline.org/patients/support-groups. To register for this online support group, please email info@natfonline.org.

International Society on Thrombosis and Haemostasis Meeting

July 20, 2018, Dublin, Ireland – “New Strategies to Prevent CV Events After Hospital Discharge”

European Society of Cardiology Meeting

August 27, 2018, Munich, Germany – “Preventing PE & DVT in Heart Failure and Other Medically Ill Patients: An Innovative Action Plan”

2018 NATF Summit

September 26, 2018 – The Fairmont Copley Plaza

This special dinner program will provide a comprehensive review of the most important changes and advances impacting the care of patients who have, or are at risk for, diabetes and cardiovascular disease. Updates in treatment, diagnosis, and prevention will be given by leading experts in the fields of endocrinology, cardiology, and nephrology. This CME accredited program is for any healthcare provider involved in the care of patients with, or at risk for developing, diabetes and cardiovascular disease, and chronic kidney disease.

Celebration of Gratitude

October 25, 2018 – The Museum of Science Boston

NATF would like to invite you to join us for the 2018 Celebration of Gratitude, NATF's premier fundraising event. It will be an exciting night of inspiration, fun, and discovery. Guests will have exclusive access to the Museum of Science's Blue Wing and will get to spend the night exploring the Wing's variety of eye-opening exhibits, attending a cocktail reception, seated dinner, and dessert reception.

For more information on any of these events, please email events@natfonline.org. We look forward to hearing from you!



PATIENT PERSPECTIVE

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While I was training, I was having some soreness in my calf and leg. Initially, I thought I had a pulled muscle. I kept training and completed the Pan-Mass Challenge. After, I was away on vacation, relaxing on the beach, and I saw a red sore spot on my ankle. That's when I decided to seek out treatment.

Q: What type of treatment did you receive?

First, I went to my primary care doctor. They sent me for additional testing. I was very happy that my primary care doctor recognized what it might be and made some good recommendations on specialists and treatments.

I went to a specialist, but it was hard to get a definitive answer on what my diagnosis was. I was getting some mixed messages about how to handle it, what type of medications I should be on, and whether I should keep cycling and exercising.

Q: Do you know what caused your blood clot?

My father had multiple blood clots. It started out when he was in his 30's. My grandparents on both sides of the family also had blood clots. So, there is a family history there, but when I went through the tests, no one could point to a specific genetic connection. That felt frustrating when I didn't get any answers.

I still don't know why it happened. I didn't suffer from any physical trauma. I haven't been able to pinpoint a specific event that caused it. When I was looking for a reason, I wasn't getting clear answers. It really gave me a lot of unknowns.

Q: How did you feel after your blood clot?

I didn't understand why it happened, because I felt like I was in excellent shape. It froze me. I didn't know if all of the working out I had been doing had caused it. After my blood clot, I stopped exercising. I didn't work out or go cycling. I put on about 20 pounds between August and February.

I was really frustrated that I wasn't getting clear answers. That's when I decided that I should do some research on my own. In doing that, I stumbled across NATF, the blood clot support group, and Dr. Sam Goldhaber. I decided to sign up for support group to see what it might lead to and made an appointment to see Dr. Goldhaber.

Q: What was your experience with support group like?

I wasn't sure what to expect from the support group or Dr. Goldhaber. But, I am very happy with what I found there.

What I found was the whole concept that I am not alone in this. A lot of others are dealing with it. It really helped to listen to other people's stories and hear about how they were affected by their blood clots and how they worked through it.

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ZEBRAFISH

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"You might notice a big difference between a fish heart and a human heart. One of the big differences is that the zebrafish heart only has two chambers. It has one ventricle and one atrium. Humans have four. But, there are a lot of similarities," explained Dr. Kithcart. "The electrical



Dr. Kithcart explaining the similarities between zebrafish and humans

conduction in the heart is very similar to that in a human, so we can study arrhythmias, like atrial fibrillation."

"The vascular system is also similar," he continued. "They have an aorta, just like us. They also have a vein. We can study things like atherosclerosis and deep vein thrombosis. In the case of a fish, they don't have limbs, but they have major veins in the tail, so we can study blood clots in the veins."

LIFE IN THE LAB

In the lab, the zebrafish are raised in nursery tanks to start their lives and then are moved to new tanks when they reach 3 months of age. That is when they are considered fully developed and start to lay eggs.

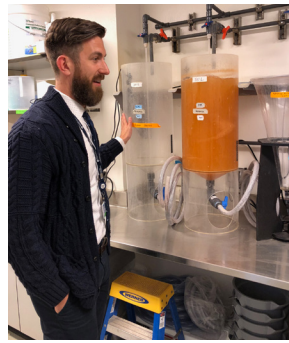
Their tanks are designed to mimic their natural environments.

"Zebrafish have been raised in lab environments for decades now. So, we're very used to being able to raise them in an artificial environment, but we try to mimic, as much as possible, their native environment," explained Dr. Kithcart.

The zebrafish lab at Brigham and Women's maintains the lab at a warm 78 degrees, closer to the fish's natural temperature, and they have a strict light cycle, where the lights are turned on at 8 am and off at 10 pm. This light cycle mimics the light cycle of the fish's natural environment. Their diet consists of brine shrimp prepared in the lab.



Newly hatched zebrafish



Dr. Kithcart with the mixture of fish food

GENOME EDITING

In the zebrafish lab, Dr. Kithcart uses genome editing to study cardiovascular health. Using a technology called "CRISPR," researchers like Dr. Kithcart can change the genes of the fish so that they express different traits. CRISPR stands for "Clustered Regularly Interspaced Short Palindromic Repeats." It works by targeting and editing specific pieces of DNA, which leads to changes in

how different genetic traits are expressed.

It all starts when the fish egg is first fertilized and exists as a single cell.

"When the egg is fertilized at the one cell stage, we can inject something into that single cell and it will propagate into all of the cells," explained Dr. Kithcart. "CRISPR is what I use right now. We use it to edit the genome. What that does is it goes in and targets a specific area of the DNA, manipulates it, and then that DNA change is passed along to every single cell down the line. That's why we do it at the one cell stage."

By using CRISPR and other forms of genetic manipulation, the Brigham and Women's lab has been able to create several different strands of zebrafish to help study cardiovascular health.

Casper Zebrafish

Researchers can modify the appearance of the fish using CRISPR. One example of genetically modified zebrafish are the Casper zebrafish. The Casper fish, named after Casper the Friendly Ghost, have been manipulated and bred to be transparent. Researchers can easily observe the insides of the fish, including the cardiovascular system.

"These fish in particular are useful for studying things like



The Casper zebrafish

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Bring Support to your Community!

NATF is looking for patients or healthcare providers that would like to start a blood clot support group in their area.

With short appointment times, it can be difficult for patients to get the answers and support they need to understand and process their blood clot diagnosis. Starting a blood clot support group with the North American Thrombosis Forum can help!

Don't take our word for it! One Boston support group member described their experience as, "Very encouraging. It became very clear that life after a blood clot is certainly a possibility and a real positive possibility."

If you, or someone you know, may benefit from starting a blood clot support group, email kmeredith@natfonline.org to learn more.



DOAC Deep Dive: Betrixaban

For the past several decades, warfarin has been the go-to [anticoagulant](#) for doctors, but new treatments have recently emerged in the form of [direct oral anticoagulants](#) (DOACs). DOACs are considered more effective and safer than warfarin, especially in relation to serious bleeding episodes. These anticoagulants include [apixaban](#), betrixaban, [dabigatran](#), edoxaban, and rivaroxaban.

NATF is dedicated to offering readers a closer look at each DOAC in order to empower patients to make informed healthcare decisions. In this issue of *The Beat*, NATF takes a closer look at betrixaban:

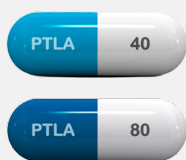
WHAT IS BETRIXABAN? WHAT MAKES IT UNIQUE?

Betrixaban, also known as Bevyxxa, is the newest DOAC on the market. It is similar to the other DOACs, but it has a unique purpose: it's specifically approved to protect medically ill hospitalized patients from developing a blood clot. Patients on betrixaban start with an initial single oral dose of 160 mg and follow that up with a once daily dose of 80 mg for 35 to 42 days. This helps to protect them while they are in the hospital and during the initial period after they've been discharged.

Did you know that these hospitalized patients are at a very high risk for developing a blood clot in their lungs (pulmonary embolism or PE) or in their legs (deep vein thrombosis or DVT)? According to the Surgeon General, hospital-acquired PE is the most common and most preventable cause of PE.

Betrixaban was approved for treatment on June 23, 2017, after being fast-tracked by the FDA. This fast-tracked designation was the result of how high the need was to protect these vulnerable patients.

"The fast track designation was applied for the high unmet need," explained Dr. C. Michael Gibson, an investigator for the APEX trial. "Despite all of the currently available agents, there are still high rates of VTE (venous thromboembolism) development in medically ill patients."



Betrixaban capsules

The APEX trial was the key trial that proved betrixaban could help these patients. The trial was a randomized, double-blind, multinational clinical trial that compared extended duration betrixaban to enoxaparin, the standard treatment for these patients.

In the trial, 7,513 patients were randomized to receive betrixaban for 35 to 42 days, with a placebo injection for 6 to 14 days, or an injection of enoxaparin for 6 to 14 days, with a placebo pill for 35 to 42 days. In the end, the trial showed fewer adverse events in patients on betrixaban than those on enoxaparin.

In addition to serving a unique population, betrixaban has several other properties that set it apart from the rest of the DOACs.

"First, it has a longer half-life of nearly one day, where the other agents are half that or less," explained Dr. Gibson. "This means the drug can truly be given once a day. The other distinguishing property is the very, very low renal clearance of betrixaban. It's not cleared by the kidney, which makes it particularly attractive for elderly patients who have impaired renal function."

HOW DOES IT WORK?

Betrixaban works by stopping a system known as the "clotting cascade." The clotting cascade is the system that causes blood to clot. This comes in handy when you are bleeding, but it causes problems when blood clots form where they shouldn't, such as the lungs or limbs. Betrixaban interrupts the clotting cascade by binding to a factor Xa molecule, stopping the clotting process from continuing.

"All roads to forming a blood clot lead through factor Xa. It doesn't matter how you kick the process off, you have to go through factor Xa. This drug blocks that step," summarized Dr. Gibson.

WHAT ARE THE RISKS?

As with all of the DOAC medications and blood thinners, patients taking betrixaban are at risk for bleeding. Patients and their physicians need to consider this when deciding if this is a medication they should be on.

"Every patient is different. Physicians will need to weigh the patient's risk of bleeding versus their potential magnitude of benefit," explained Dr. Gibson, stressing the importance of reading the drug's package insert.

"Betrixaban has been studied in 7,000 patients and looked to be quite safe. There was no excess major bleeding with the drug," explained Dr. Gibson, referencing the APEX trial. "There was some excess risk of minor to moderate bleeds. That's something patients will have to weigh as they make a decision. Do they want to prevent a blood clot going to their lung, or do they want to have light bleeding? I think patients and physicians will have to work together and engage in shared decision making to make the right choice for the right patient."

Patients with severe renal impairment or those on P-glycoprotein inhibitors should talk to their doctor about receiving the recommended lower dose of the drug.

It is important to take betrixaban exactly as prescribed. If you have missed a dose of betrixaban, see the drug's package insert to determine your next steps.

If you think that betrixaban may be a good option for you, talk to your doctor about your options. Only your personal healthcare provider can give you the individualized medical advice you need. This DOAC Deep Dive is for informational purposes only.



PATIENT PERSPECTIVE

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The group shared their stories, similar to mine, about how they dealt with exercise. They were adamant that I start biking and exercising again. Dr. Goldhaber also encouraged me to start exercising again. He said that anything that is good for my cardiac health, is good for me.

Q: How did this affect you?

The good news is, I started working out the very next day. I got back to the gym and started cycling again. I've even signed up again for the Pan-Mass Challenge and a triathlon. I'm training about 6 days a week and I've lost 15 pounds. I'm back to cycling about 20-25 miles, multiple days a week, swimming, and running. It allows me to clear my mind.

Q: Do you have any message you'd like to share with other patients?

My message to anybody else dealing with blood clots would be that, if you are feeling anxious or scared, you are probably not alone. You're not the first person to go through this. Try to find a support group or other means to be able to talk with other patients. Most importantly, prioritize your health with proper exercise and eating habits. You may find benefits you wouldn't even expect.

Are you looking for support? Attend NATF's in-person support group in Boston or visit www.natfonline.org for information about NATF's online support groups.

Thank you, Mark, for sharing your story! If you would like to support Mark's Pan-Mass Challenge ride, visit: <https://egifts.pmc.org/MS0609>.

Are you inspired by stories like Mark's? You can help patients similar to Mark by starting a support group in your community. Join us in the fight against blood clots and email: info@natfonline.org.



ZEBRAFISH

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The FlkGFP zebrafish under a microscope

blood clots," commented Dr. Kithcart. "I use these fish to look at blood clots forming because I can look right through the fish. You can look under a microscope and actually see a blood clot forming."

Glowing Zebrafish

Several strands of zebrafish in Brigham and Women's lab have been genetically modified using transgenic manipulations to glow under the right lighting. Researchers use this lighting to observe the fish under a microscope. Two of these strands are known as IGM GFP and FlkGFP.

"GFP stands for green fluorescent protein," explained Dr. Kithcart, addressing the IGM GFP strand. "These fish genetically express a green fluorescent protein on all of the cells that express IGM, which are B cells. All of the B cells in this line of fish will be green."

B cells are a form of white blood cell that play an important role in the immune system.

"Another fish studied with GFP are FlkGFP," he continued. "That means there's green fluorescent protein expressed on all of their blood vessels. Blood vessels are, of course, very important in clot formation. I use these fish a lot to look at how clots are forming."

High Cholesterol Diet Zebrafish

In addition to genetically modifying the fish for research, researchers can change the fish's diet and environment to study different topics. Some of the zebrafish are used to study the effects of an unhealthy diet on the cardiovascular system.

"We have fish that are being fed a high cholesterol diet. We feed them an 'Americanized' diet that is about 4 percent by weight in cholesterol. It would be very similar to having a Big Mac 5-6 times a day," said Dr. Kithcart.

"They're much bigger," he continued, describing the adult zebrafish who grew up on the high cholesterol diet. "After being fed a high cholesterol diet for a couple of years, these fish are huge. They're unhealthy. They get atherosclerosis just like any human would, who had been on that type of diet for that long. They tend to die of early disease."

LOOKING FORWARD

As research on these fish continues, they represent an endless opportunity for innovation and new discoveries. From cancer to aging, blood clots to heart attacks, these fish will help the scientists of the future to discover new treatments and perhaps even answers to some of medicine's most pressing questions.

Thank you, zebrafish, for opening the door for discovery.



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