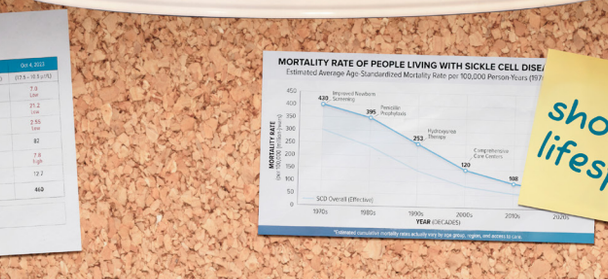

low hemoglobin /anemia

shorter lifespan

fatigue

organ damage

YOU KNOW ABOUT PAIN CRISES, BUT

THERE'S ONGOING **SILENT DAMAGE** HAPPENING IN SICKLE CELL DISEASE

HEMOLYSIS

THE BREAKDOWN OF RED BLOOD CELLS

Hemolysis is the early breakdown of red blood cells, leading to low hemoglobin/anemia, fatigue, organ damage and a shorter lifespan

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DON'T OVERLOOK THE CLUES.

TALK TO YOUR DOCTOR ABOUT HEMOLYSIS

AND ITS DEVASTATING IMPACT ON SICKLE CELL DISEASE.

Ayana
sickle cell warrior

SCD Warriors were compensated for their participation.

What is sickle cell disease?

Sickle cell disease is a complex red blood cell disorder. In people living with sickle cell disease, there are changes to red blood cells that can cause damage throughout the body

- Red blood cells become misshapen into a "sickle shape," like a crescent moon:

Healthy red blood cell

Sickled red blood cell

- Sickle cell disease can lead to serious complications over time, like organ damage

Who's at risk for sickle cell disease?

- Sickle cell disease affects people from many backgrounds
- In the United States, sickle cell disease most commonly affects Black and African American people
- Sickle cell disease also affects Hispanic and Latino people and those of Middle Eastern, Mediterranean, and South Asian descent

Sickle cell disease can impact quality of life and may lead to serious complications that can impact long-term health.

There are many types of sickle cell disease, but all are serious and have an increased risk of complications

The type of sickle cell disease you have depends on your genes

In sickle cell disease, there is a change in one of the genes that makes a part of hemoglobin (Hb). Hemoglobin is a protein in red blood cells. This genetic change affects how Hb behaves.

Type of sickle cell disease	How common is it?*
HbSS	About 75% of people with sickle cell disease
HbSC	About 18% of people with sickle cell disease
HbS beta-plus thalassemia	About 4% of people with sickle cell disease
HbS beta-zero thalassemia	About 2% of people with sickle cell disease

What are genes?

- Genes are the instructions the body uses to make proteins. These instructions are like a recipe
- When a gene is changed, it is called a gene variant. Think of a variant like a variation in the recipe

*A large international study of 674 people with sickle cell disease published in 2011 looked at the genetic types in people of mainly African descent living in the Americas and the UK.

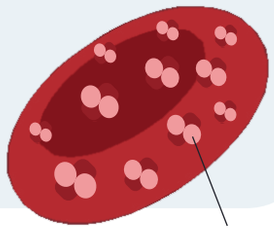
No matter the type, all forms of sickle cell disease are considered serious. This is because **all forms of sickle cell disease can lead to life-threatening complications**.

Sickle cell disease begins with sickling. Here's how it happens

In sickle cell disease, the body makes a type of hemoglobin called hemoglobin S (HbS). Hemoglobin is a protein in red blood cells that carries oxygen from the lungs and delivers it throughout the body.

Healthy hemoglobin

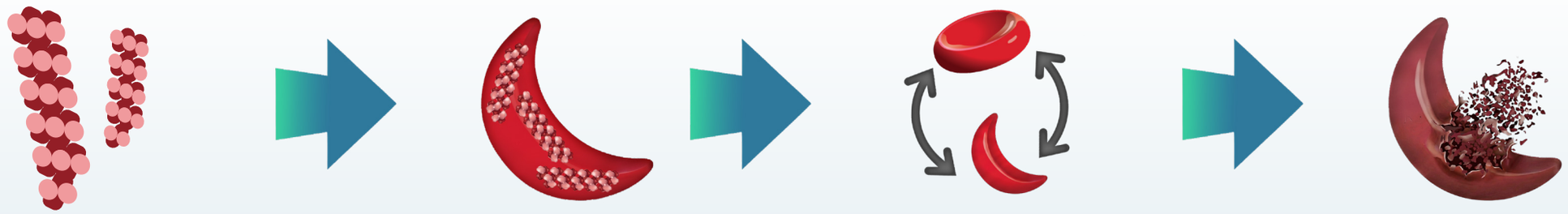
Healthy hemoglobin stays flexible whether it is carrying oxygen or not.



Unhealthy hemoglobin

The genetic change in HbS causes the hemoglobin to link together.

The sickling process



Unhealthy hemoglobin molecules link together

When red blood cells release oxygen, unhealthy hemoglobin molecules link together **(polymerization)**, and form into stiff rods inside the cell.

Red blood cells change shape

These rods bend red blood cells into a sickle shape.

Red blood cells sickle and unsickle in a cycle

As red blood cells release and pick up oxygen, they repeatedly sickle and unsickle until they become permanently sickled over time.

Red blood cells become fragile and break down (hemolysis)

Fragile red blood cells cannot withstand the stress of repeated sickling and unsickling and breakdown.

Repeated sickling and unsickling puts stress on red blood cells. This leads to red blood cells breaking down.

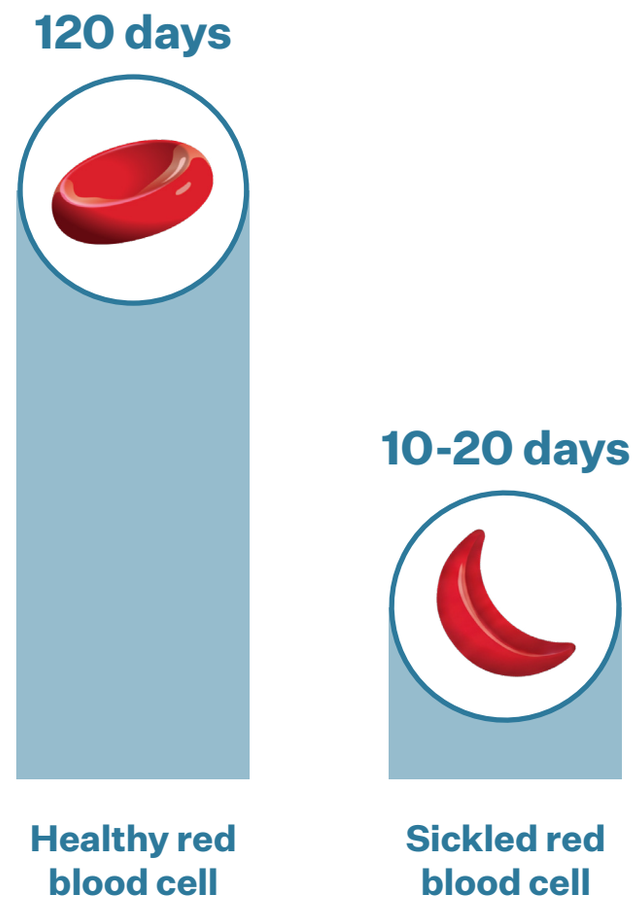
Images are for illustrative purposes only.

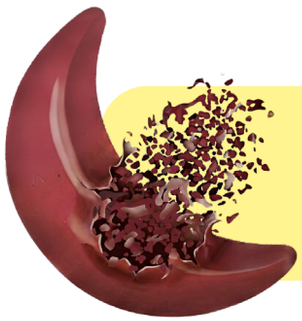
Why red blood cells in sickle cell disease don’t live as long (hemolysis)

Energy plays a key role in red blood cell health

- Red blood cells make energy. This energy is called ATP (adenosine triphosphate). **Energy from ATP helps red blood cells keep their shape and work the way they should**
- **Red blood cells don’t work as well in people with sickle cell disease.** That’s because they keep changing shape and can’t carry oxygen as well as healthy red blood cells
- **Sickling and unsickling puts stress on red blood cells.** In sickle cell disease, red blood cells do not have the energy they need to work properly and survive
- Because of this, **red blood cells can break down early and don’t live as long**

How long can red blood cells live in your body?





With less energy (ATP) and more stress, **red blood cells in sickle cell disease** break down early. This is called **hemolysis**.

What happens in sickle cell disease?

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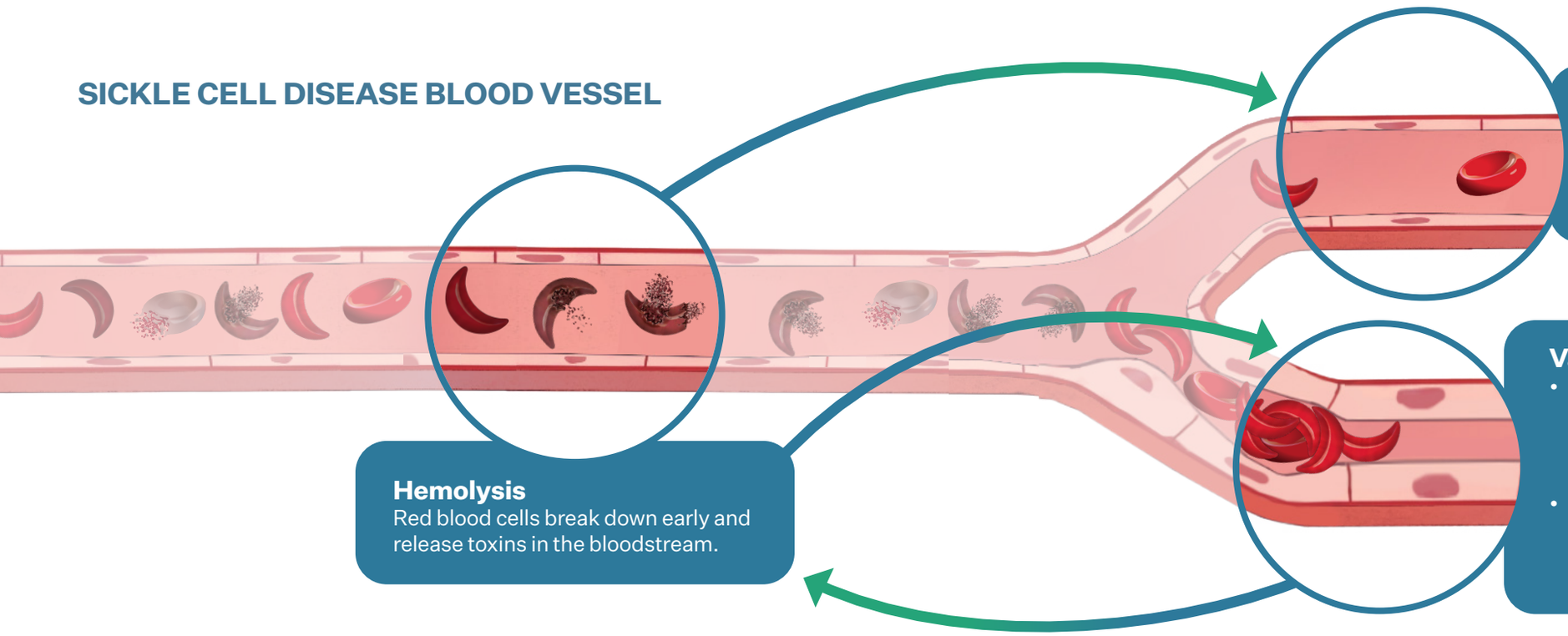
HEALTHY BLOOD VESSEL

SICKLE CELL DISEASE BLOOD VESSEL



Hemolytic anemia
As a result of hemolysis, there are fewer red blood cells and your organs and tissues don't get enough oxygen. This is called hemolytic anemia.

Vaso-occlusion

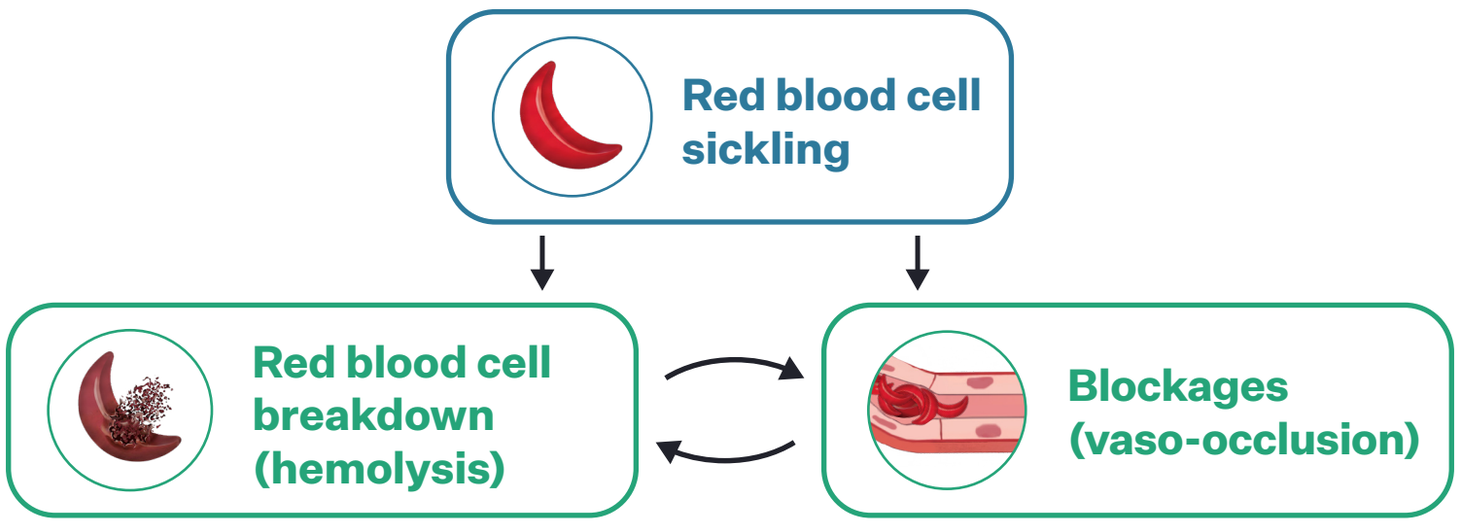
- Toxins released from red blood cell breakdown cause inflammation and damage to blood vessels. Blood vessels become stickier and narrowed
- Sickled cells clump together and stick to blood vessels and cause blockages. Blocked blood vessels reduce oxygen flow to the body and cause sickle cell pain crises

Hemolysis
Red blood cells break down early and release toxins in the bloodstream.

Hemolysis causes red blood cells to break down early in the bloodstream, which can lead to **hemolytic anemia** and contributes to blockages in the blood vessels, called **vaso-occlusions**.

Red blood cell breakdown (hemolysis) contributes to blockages (vaso-occlusion)

Sickling leads to blockages and early red blood cell breakdown



Vaso-occlusions happen when sticky, sickled red blood cells clump together in the blood. This creates a “traffic jam” that keeps oxygen from being delivered throughout the body

- Vaso-occlusions can cause extreme pain (pain crises or vaso-occlusive crises). These intense pain crises are what most people think of when they think of sickle cell disease
- When red blood cells break down, blockages are more likely. These blockages can cause even more red blood cell breakdown
- Blockages result in less oxygen being transported throughout the body which can lead to organ damage

Blockages (vaso-occlusions) can cause extreme pain crises. Like **hemolysis**, blockages can lead to organ damage.

Organ damage can happen even in the absence of frequent vaso-occlusive crises (VOCs)

Frequency of health complications and organ damage in sickle cell disease

	People with sickle cell disease with **0-1 VOC** per year (n=45)
Retina damage (retinopathy)	60%
Gallstones (cholelithiasis)	60%
Inflammation and blockages in the lungs (acute chest syndrome)	50%
High blood pressure in the lungs (pulmonary hypertension)	47%
Kidney(s) leaking blood protein (microalbuminuria)	36%
Death of bone tissue (osteonecrosis)	24%
Kidney failure (renal failure)	21%
Leg ulcer	11%
Stroke	11%
Prolonged, painful erection (priapism)	9%

Based on a 2006 study of 104 adults with main gene types of sickle cell disease in the Netherlands. Adults were screened for sickle cell disease-related complications twice a year in the 7-year follow-up study.

Hemolysis leads to hemolytic anemia (low hemoglobin) and puts your organs at risk

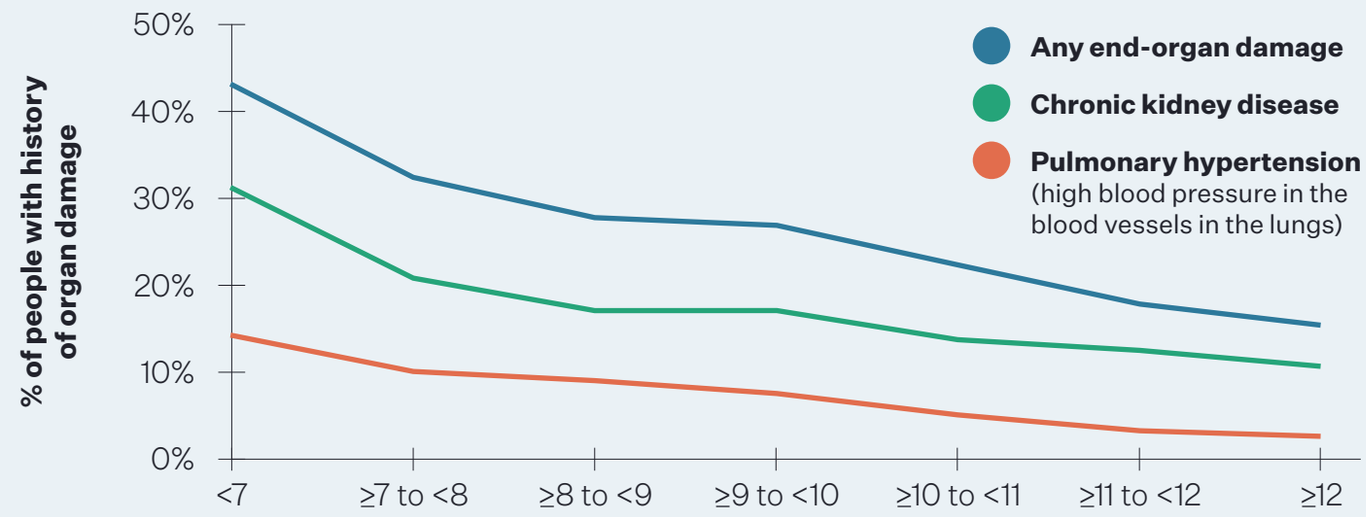
Hemolysis can lead to health problems like:

- Hemolytic anemia (low hemoglobin)
- Yellowing of the skin and whites of the eyes (jaundice)

Complications from hemolysis can cause more damage to your body over time:

- People living with sickle cell disease with low hemoglobin face a 3x-higher risk of organ damage

Lower hemoglobin levels are linked to higher rates of organ damage

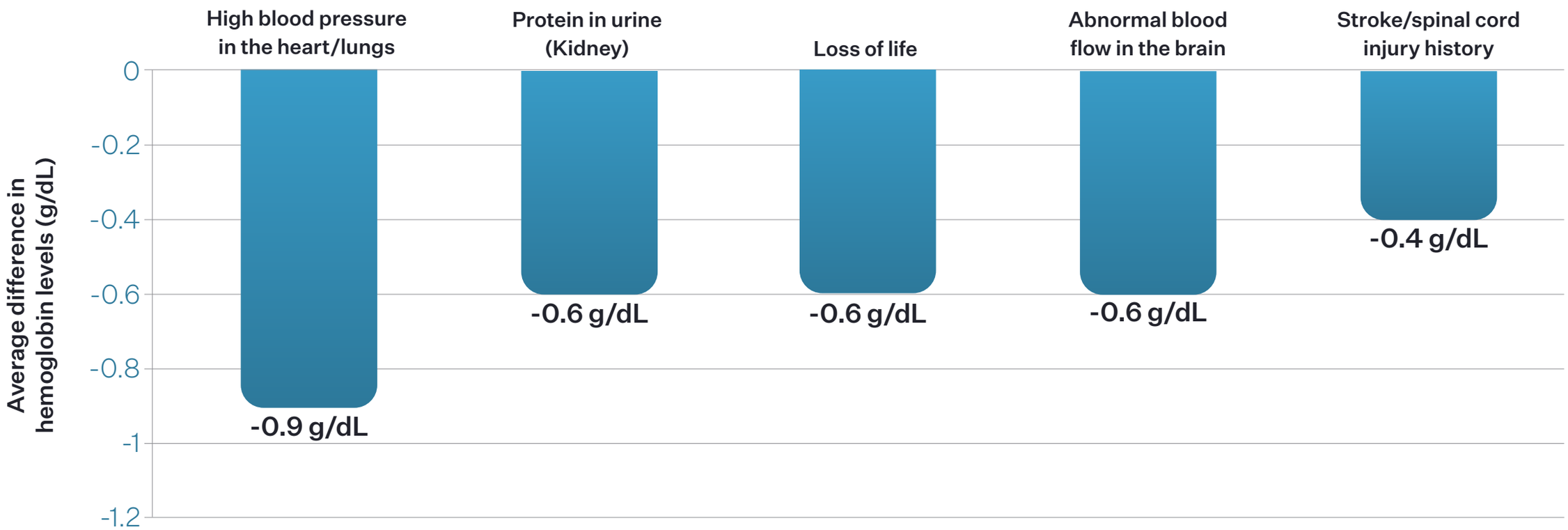


This study examined health insurance records from January 1, 2012, through July 31, 2020, to better understand how hemoglobin levels are related to organ damage in people aged 12 years and older living with sickle cell disease. The study included more than 16,000 people aged 12 years and older who had at least 1 hemoglobin result. Researchers reviewed patients' records for one year after each test to see if any organ damage occurred.

Hemolysis, leading to hemolytic anemia (low hemoglobin), can damage the body over time—**even when you don't feel it**.

Even small decreases in hemoglobin are associated with increased risk of organ damage and risk of shorter lifespan

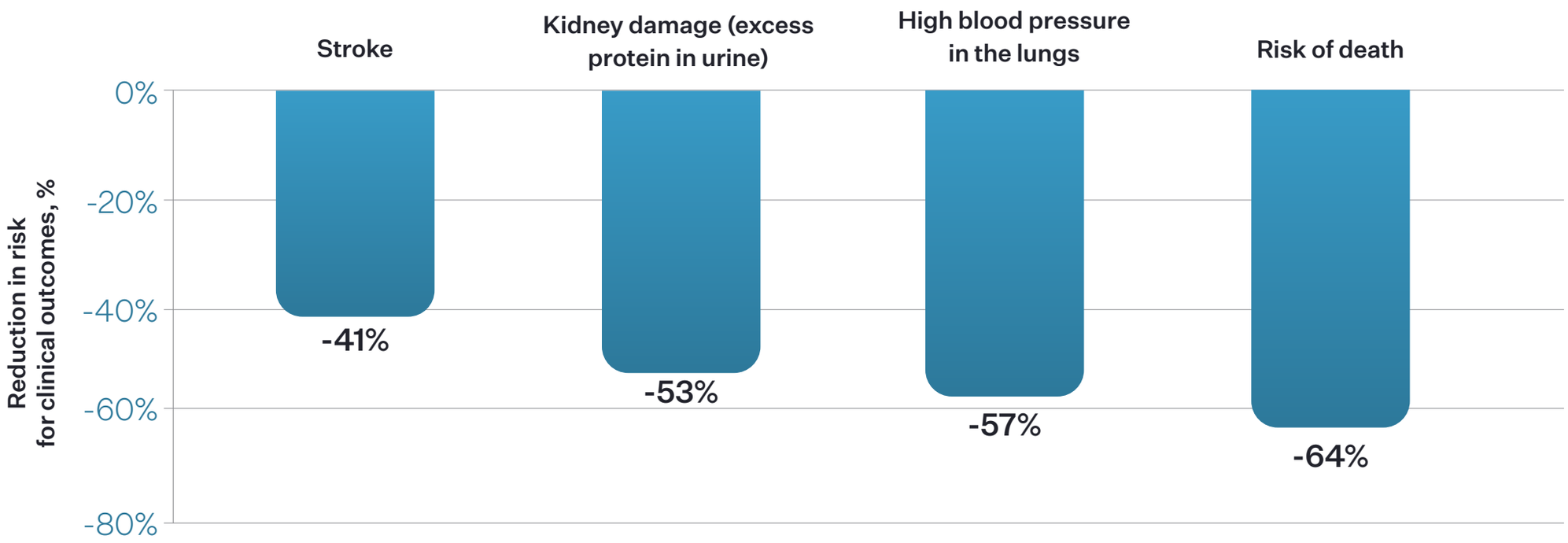
Average difference in hemoglobin levels for people with complications vs those without



This analysis screened 2820 publications (January 1, 1998 to February 26, 2019) and included 41 studies examining hemoglobin concentration and clinical outcomes in people with sickle cell disease. Studies covered various types of genes and therapies, and all the data were looked at together.

Increasing hemoglobin by at least 1 gram per deciliter (g/dL) is associated with lower risk of organ damage and longer lifespan

Predicted decrease in risk for clinical outcomes associated with a ≥1 g/dL increase in hemoglobin



This analysis screened 2820 publications (January 1, 1998 to February 26, 2019) and included 41 studies examining hemoglobin concentration and clinical outcomes in people with sickle cell disease. Studies covered various types of genes and therapies, and all the data were looked at together to also predict if better outcomes might be associated with increased hemoglobin concentration.

Hemolysis and low hemoglobin can cause both short-term and long-term organ damage

Organ damage:

Occurs throughout the body and can occur without any symptoms at all

Can happen even when there is no pain

Is progressive, which means it worsens over time

Can be life-threatening

Organ damage is a leading cause of death in people with sickle cell disease. Working with your doctor to establish a regular monitoring plan may help catch problems early.

Hemolysis and low hemoglobin affect more than long-term health

Hemolysis and hemolytic anemia impact daily living and quality of life. For example, hemolysis and low hemoglobin in sickle cell disease can cause:

Fatigue, because your tissues and organs aren't getting enough oxygen

General **weakness** felt all over your body

Brain-related issues, such as **memory loss**, **learning challenges**, or **brain fog**

Shortness of breath that's long-lasting, which can **limit movement**

Impotence from repeated erections that are long-lasting and painful (priapism)

It's important to **recognize and report** new symptoms that you experience to your care team. This can help them—and you—get a **fuller picture of your health**.

Monitoring can help you keep tabs on hemolysis and low hemoglobin

There are a few ways to directly and indirectly monitor hemolysis and hemoglobin

Levels can be checked by your healthcare provider with a simple blood draw.

Bilirubin Bilirubin is created when red blood cells break down early as part of hemolysis.	**Reticulocytes** Reticulocytes are immature red blood cells that are made in the bone marrow. After being released into the bloodstream, reticulocytes mature into red blood cells.	**Hemoglobin (Hb)** Hb levels are checked to monitor for anemia.

• Bilirubin is also responsible for yellowing of the skin and white of the eyes. This is known as jaundice
• High bilirubin signals that hemolysis is occurring
• Normal bilirubin levels are between 0.1 and 1.2 milligrams per deciliter (mg/dL), while levels seen with hemolysis are typically 2 to 3 mg/dL
	• When too many red blood cells are breaking down early (hemolysis), the body tries to replace them. This increases the amount of reticulocytes
	• This is a signal that the bone marrow is making new red blood cells to replace those lost from hemolysis
	• Normally, the % of cells that are reticulocytes versus mature red blood cells range between 0.5% and 2.5%. With hemolysis, the % is usually above 2.5%
		• Healthy Hb levels in adults without sickle cell disease:
		  • Males: 14-17 grams per deciliter (g/dL)
		  • Females: 12-15 g/dL
		• Hb levels are lower in people with sickle cell disease, at around 6-11 g/dL
		  • Low or decreasing Hb levels are associated with hemolytic anemia

Your doctor will keep an eye on your bilirubin, reticulocytes, and Hb and watch for changes

This can help your doctor understand how much strain sickle cell disease is putting on your body over time. Talk to your healthcare team if:

- Your symptoms suddenly change
- You feel even more tired than usual
- You notice new or worsening yellowing of your skin or eyes

Work with your doctor to **monitor hemolysis and hemoglobin** and **establish appropriate levels** based on your own individual needs.

Disease-modifying therapies for sickle cell disease that address hemolysis and low hemoglobin are needed

Most common disease-modifying medications focus on preventing pain crises.

They include:

Hydroxyurea

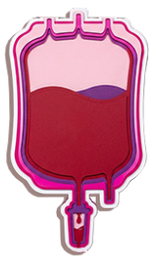
- An oral medicine that helps the body make fetal hemoglobin to help prevent sickling of red blood cells. It also helps red blood cells flow more easily through the blood

Crizanlizumab

- A medicine that is given through a vein (IV infusion). This treatment blocks a protein that causes red blood cells to stick together and to the blood vessel lining

L-glutamine

- A powder mixed with water or food. This medicine gives your body glutamine and is thought to help protect sickle cells from damage



Transfusions

Transfusions are sometimes used when hemoglobin levels drop significantly or to address certain sickle cell disease complications. **Transfusions add healthy red blood cells from a donor into your body.** Because your body has to process this new blood, your care team will keep an eye on your iron levels and any reactions to donated blood.

The future of sickle cell treatment

Scientists are researching new disease-modifying medicines that focus on red blood cell health and target hemolysis.

IV=intravenous.

Supportive tips that can be helpful

Taking folic acid
Supports the body in producing new red blood cells

Staying hydrated
Helps the blood flow more easily through blood vessels

Getting good nutrition
Helps support hemoglobin production and prevent other complications that might worsen sickle cell disease

Getting enough rest
Gives your body time to catch up and allows your heart to not work as hard

Talk to your healthcare team about these and other ways to help manage sickle cell disease.

Discover myAgios® Patient Support Services

What is myAgios Patient Support Services?

myAgios is a customized support program for people living with sickle cell disease, designed to provide personalized education and treatment support.

For individualized sickle cell disease education, you can talk to an Agios Clinical Educator (ACE).

An ACE helps with:

One-on-one disease education and/or support in understanding management options through in-person or virtual interactions.

Access to disease-state education and resources to support informed decision-making and productive conversations with your healthcare provider.

Connecting with educational programs, webinars, advocacy organizations, and other community resources.

Learn about sickle cell disease and find support and resources.

Connect with an Agios Clinical Educator (ACE) by calling 1-877-77-AGIOS (1-877-772-4467).

ACEs do not provide medical advice. For medical advice or treatment-related questions, please talk to your healthcare team.

Now that you've put together the clues to get a fuller picture, talk to your doctor about hemolysis and its impact on sickle cell disease

Understand hemolysis

Hemolysis is the quiet, early breakdown of red blood cells.

Hemolysis can:

- lead to hemolytic anemia (low hemoglobin), fatigue, and other impacts on daily life
- lead to life-threatening organ damage

Work with your healthcare team

- Ask about hemolysis
- Ask about your lab results
- Ask how hemolysis is being monitored over time

This can help identify changes in your health and support informed decisions about care.

Watch for advances in research

Researchers continue to explore new ways to address hemolysis and improve red blood cell health in sickle cell disease.

Stay tuned for more information about developments in sickle cell disease.

For support and resources about sickle cell disease, scan the QR code to visit SickleCellClues.com. You can also connect with an Agios Clinical Educator (ACE) by calling 1-877-77-AGIOS (1-877-772-4467).