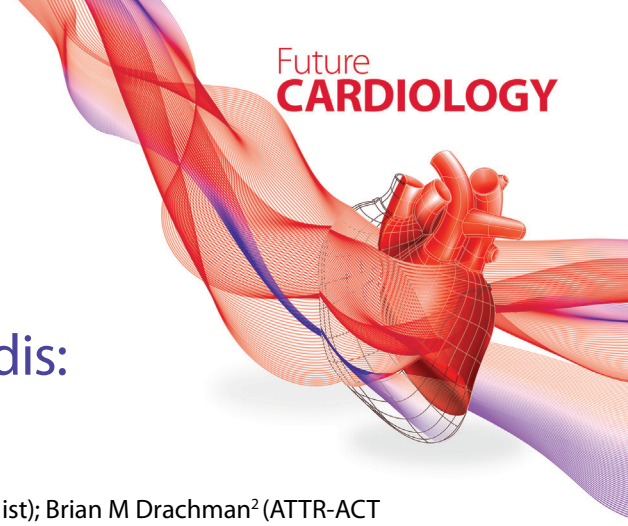
Future CARDIOLOGY

Plain Language Summary of Publication

Long-term survival in people with transthyretin amyloid cardiomyopathy who took tafamidis: a plain language summary



Perry Elliott[1] (ATTR-ACT investigator, cardiologist, and amyloidosis specialist); Brian M Drachman[2] (ATTR-ACT investigator, cardiologist, and amyloidosis specialist); Stephen S Gottlieb[3] (ATTR-ACT investigator, cardiologist, and amyloidosis specialist); James E Hoffman[4] (ATTR-ACT investigator, hematologist/oncologist, and amyloidosis specialist); Scott L Hummel[5] (ATTR-ACT investigator, cardiologist, and amyloidosis specialist); Daniel J Lenihan[6] (ATTR-ACT investigator, cardiologist, and amyloidosis specialist); Ben Ebede[7] (ATTR-ACT clinician); Balarama Gundapaneni[8] (ATTR-ACT statistician); Benjamin Li[9] (ATTR-ACT statistician); Marla B Sultan[9] (ATTR-ACT Global Clinical Lead, ophthalmologist, and rare disease specialist) & Sanjiv J Shah[10] (ATTR-ACT investigator, cardiologist, and amyloidosis specialist)

[1]University College London, London, UK; [2]University of Pennsylvania Health System, Philadelphia, PA, USA; [3]University of Maryland School of Medicine, Baltimore, MD, USA; [4]University of Miami, Miami, FL, USA; [5]University of Michigan and Ann Arbor Veterans Affairs Health System, Ann Arbor, MI, USA; [6]Washington University School of Medicine, St. Louis, MO, USA; [7]Pfizer Inc, Collegeville, PA, USA; [8]Pfizer Inc, Groton, CT, USA; [9]Pfizer Inc, New York, NY, USA; [10]Northwestern University Feinberg School of Medicine, Chicago, IL, USA

First draft submitted: 22 September 2022; Accepted for publication: 19 December 2022; Published online: 30 January 2023

Summary

What is this plain language summary about?

This summary presents the results from an ongoing, long-term extension study that followed an earlier study called ATTR-ACT. People who took part in this extension study and ATTR-ACT have a type of heart disease known as transthyretin amyloid cardiomyopathy (ATTR-CM for short), which causes heart failure and death. In ATTR-ACT, people took either a medicine called tafamidis or a placebo (a pill that looks like the study drug but does not contain any active ingredients) for up to 2½ years. So far, in the long-term extension study, people have continued taking tafamidis, or switched from taking a placebo to tafamidis, for another 2½ years. Researchers looked at how many people died in ATTR-ACT and the extension study. The long-term extension study is expected to end in 2027, so these are interim (not final) results.

How to say (double click sound icon to play sound)...

- **Amyloid:** A-muh-loyd
- **Amyloidosis:** A-muh-loi-DO-sis
- **ATTR-ACT:** uh-TRAKT
- **Cardiomyopathy:** KAR-dee-oh-my-AH-puh-thee
- **Placebo:** pluh-SEE-boh
- **Tafamidis:** tah-FAM-ah-dis
- **Transthyretin:** trans-thy-REH-tin

What did researchers find out?

In the extension study of ATTR-ACT, the risk of dying was lower in people who took tafamidis continuously throughout ATTR-ACT and the extension study than in people who took placebo in ATTR-ACT and switched to tafamidis in the extension study.

What do the results mean?

Taking tafamidis increases how long people with ATTR-CM live. People with ATTR-CM who take tafamidis early and continuously are more likely to live longer than those who do not. These results highlight the importance of early detection and treatment in people with ATTR-CM.

Note: When reading this summary, it is important to understand the following:
- This summary reports the results from a planned interim analysis of the long-term extension study that followed ATTR-ACT. This means that the extension study has not yet been completed.
- The extension study is still ongoing; its final outcomes may differ from the outcomes described in this summary.
- This summary reports the combined results of two studies. The results of individual studies may vary from these combined study results. Health professionals should make treatment decisions based on all available evidence.

Future Medicine part of fsg

Who is this article for?

People with ATTR-CM and caregivers may find that this information helps them better understand the disease and the effects of tafamidis treatment on survival. Healthcare providers may also be interested in this information if they see people who have or might have ATTR-CM.

Where can I find the original article on which this summary is based?

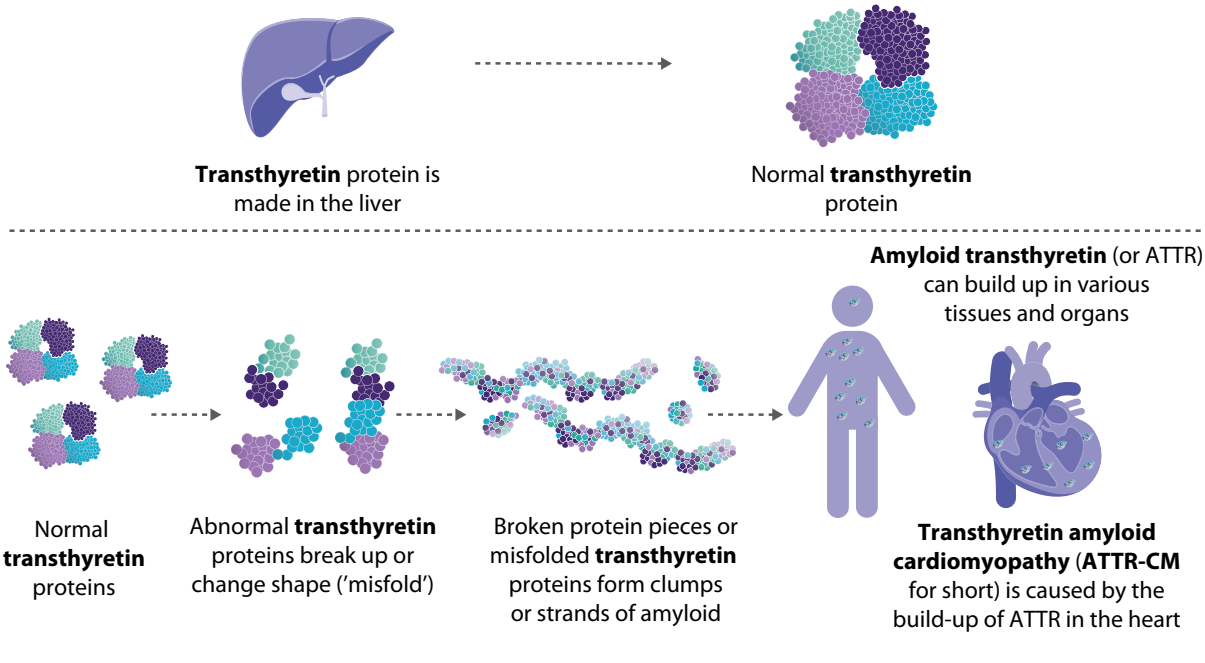
You can read the original article published in *Circulation: Heart Failure* for free at: www.ahajournals.org/doi/10.1161/CIRCHEARTFAILURE.120.008193. It is called 'Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy.'

Who sponsored these studies?

ATTR-ACT and the extension study were sponsored by Pfizer. Pfizer and the authors thank everyone who took part in the studies.

What is transthyretin amyloid cardiomyopathy?

- **Amyloidosis** is a rare disease that develops when abnormal proteins form amyloid and build up in parts of the body. Amyloid is usually associated with one type of protein that abnormally forms clumps or strands.
- **Transthyretin** is one type of protein that causes amyloidosis.



Types of ATTR-CM

Wild-type ATTR-CM is the most common type of ATTR-CM. It develops for unclear reasons, usually in people over 60 years of age.

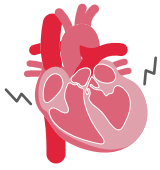
Hereditary ATTR-CM is a genetic disease. It is caused by changes in the *TTR* gene (called a gene variant or mutation) and can be passed down in families.

- Genes play an important role in how our bodies work and look.
  - Genes are short sections of DNA that carry instructions for making the proteins that cells need.
  - The DNA contains genetic information that controls activity inside a cell.

- In ATTR-CM, the heart walls become thick and stiff due to the build-up of transthyretin amyloid, so the heart has to work harder to pump enough blood around the body. Over time, as the heart grows thicker and weaker, people with ATTR-CM develop a condition called **heart failure**.
  - Heart failure develops when the heart cannot pump enough blood around the body.
  - Heart failure can range from mild to severe.
  - A simple tool developed by the New York Heart Association (NYHA) is commonly used to describe the severity of people's heart failure. The tool classifies heart failure in four classes (I, II, III, and IV) based on people's symptoms and how physically active they can be.

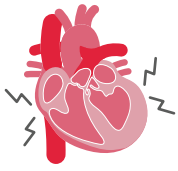
Classes of heart failure

Class I (mild)



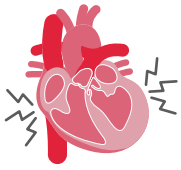
- Ordinary physical activities such as walking do not cause symptoms of heart failure, such as tiredness or shortness of breath, but clinical tests might show signs of heart failure.
- Physical activity is **not limited**.
- People are comfortable when resting.

Class II (mild)



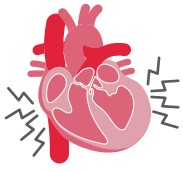
- Ordinary physical activities such as walking do cause symptoms of heart failure, such as tiredness or shortness of breath.
- Physical activity is **slightly limited**.
- People are comfortable when resting.

Class III (moderate)



- Less strenuous ordinary physical activities such as showering do cause symptoms of heart failure, such as tiredness or shortness of breath.
- Physical activity is **noticeably limited**.
- People are comfortable when resting.

Class IV (severe)

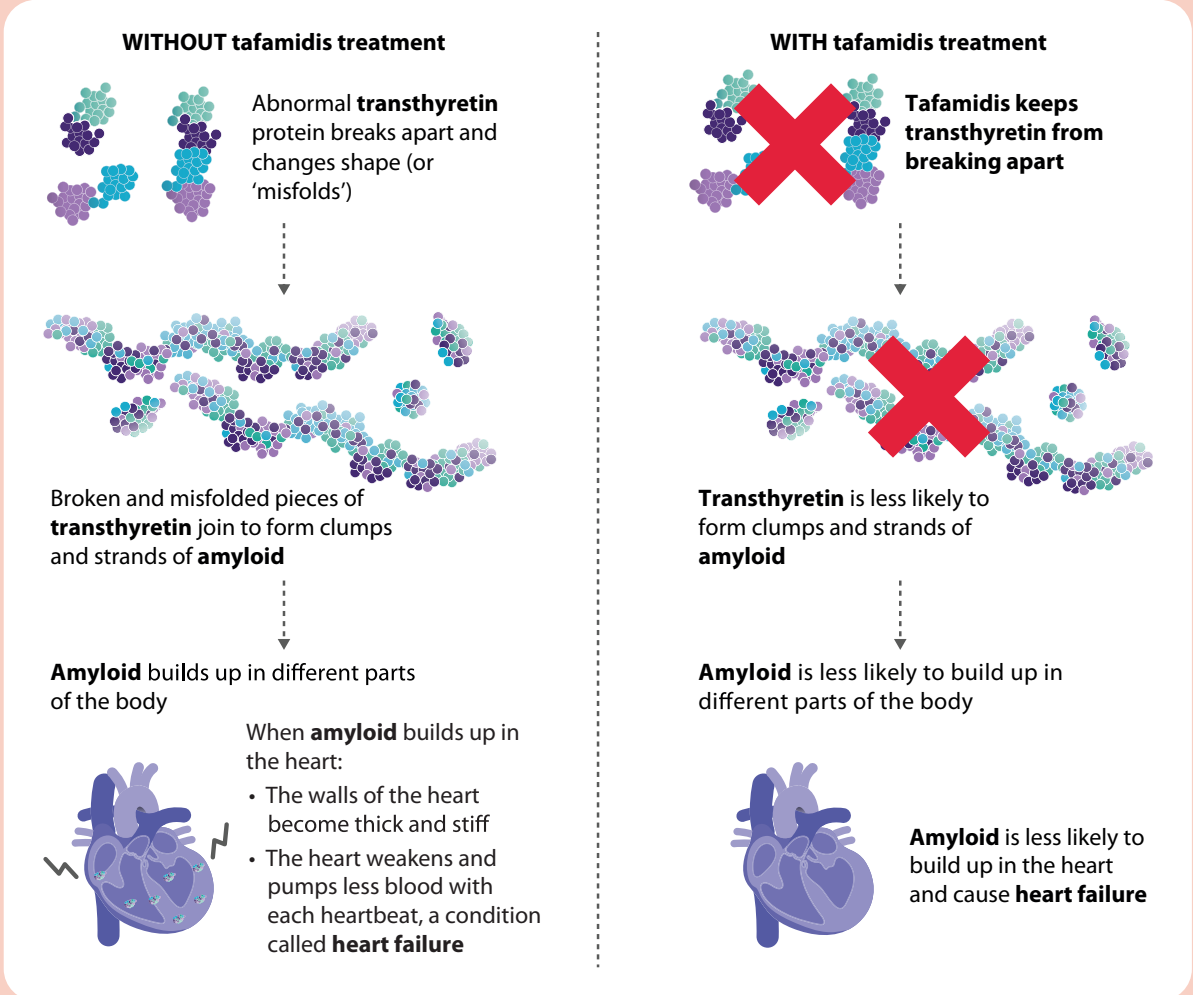


- Any physical activity causes symptoms of heart failure, such as tiredness or shortness of breath.
- Physical activity is **very limited**.
- People have symptoms when resting.

- People with ATTR-CM can also have health problems that affect other parts of their bodies, such as the kidneys, digestive system (including the stomach, and small and large intestines), and nervous system (including the brain and spinal cord).
- They may develop non-heart-related problems years before they develop heart-related problems.
  - For example, many people with ATTR-CM develop carpal tunnel syndrome before they show any symptoms of heart failure. In ATTR-CM, carpal tunnel syndrome happens when ATTR builds up in the wrist and pinches a nerve. This can cause pain, numbness, and tingling in the hand.
- People with ATTR-CM will see continuous worsening of their disease and declining health over time. This will happen no matter what kind of symptoms or type of ATTR-CM they have.

What is tafamidis and how does it work?

- **Tafamidis** is an approved medicine that helps keep transthyretin from forming amyloid.
  - As a result, amyloid is less likely to build up in the heart and cause heart failure.



What is ATTR-ACT?

- To find out if tafamidis is an effective treatment for people with wild-type or hereditary ATTR-CM, researchers conducted a study called ATTR-ACT.
  – The full name of the study is the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial.
- Before ATTR-ACT, no medicines had been approved to treat ATTR-CM. For this reason, in ATTR-ACT, researchers compared tafamidis with placebo to see if it helped people with ATTR-CM.
  – A placebo looks like the study medicine, and is taken in the same way, but it does not contain any active medicine.

People who volunteered for ATTR-ACT were randomly split into two groups:

Tafamidis 20 mg or 80 mg once a day, by mouth

Placebo once a day, by mouth

Randomly means each participant's group was decided purely by chance.

People who took part in the study:

- Were 18 to 90 years old

- Had wild-type or hereditary ATTR-CM

- Had heart failure (NYHA class I, II, or III)

After about 2½ years, researchers found that:

Tafamidis reduced people's risk of dying and being hospitalized for heart problems by about **1/3**

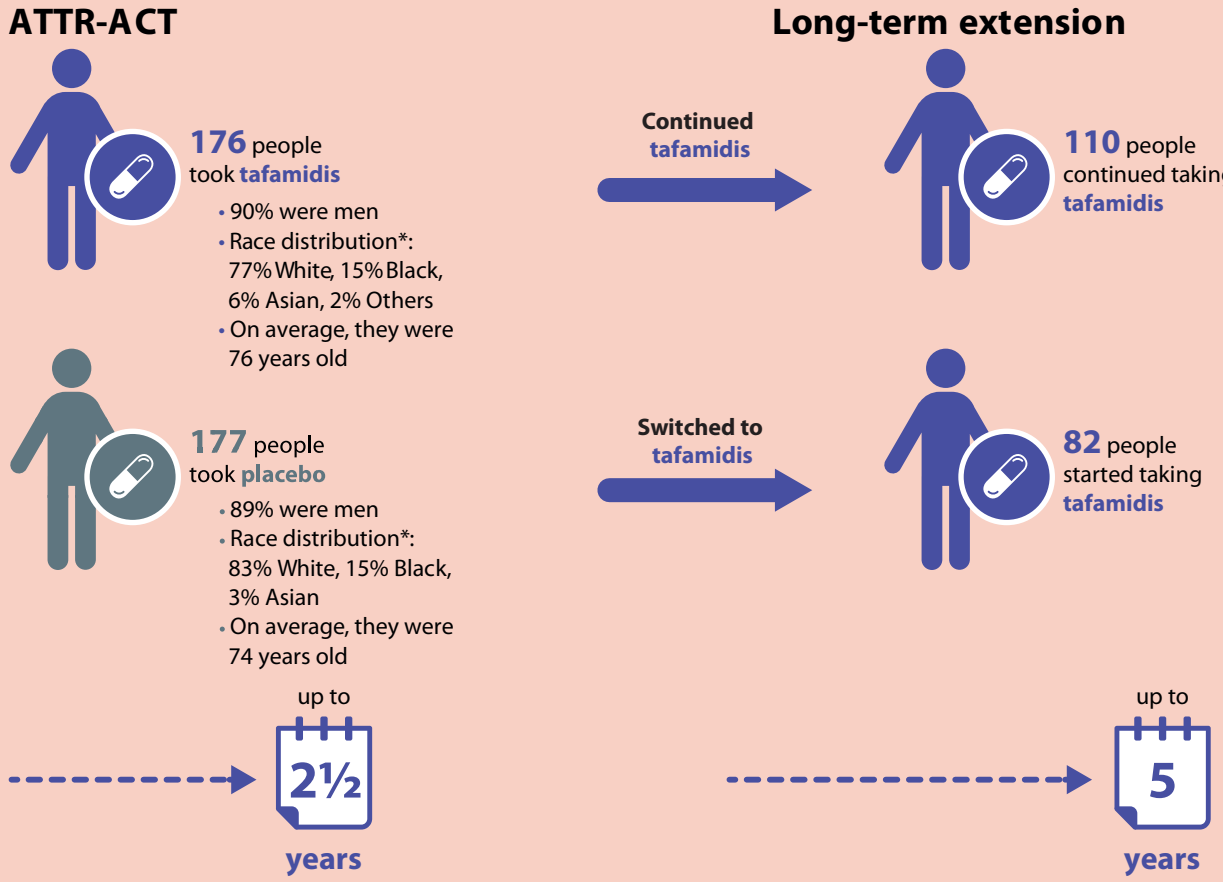
- Tafamidis was approved for the treatment of wild-type and hereditary ATTR-CM in adults based on the results of this study.
  – Tafamidis improved survival (how long people lived after their disease was diagnosed and they started treatment), quality of life, and functional capacity (their ability to carry out daily life activities) in people with ATTR-CM.
  – Tafamidis is approved to treat people with ATTR-CM in many countries around the world, including many European countries, Japan, and the United States.

ATTR-ACT registration: https://clinicaltrials.gov; unique identifier number: NCT01994889

What happened in the long-term extension study?

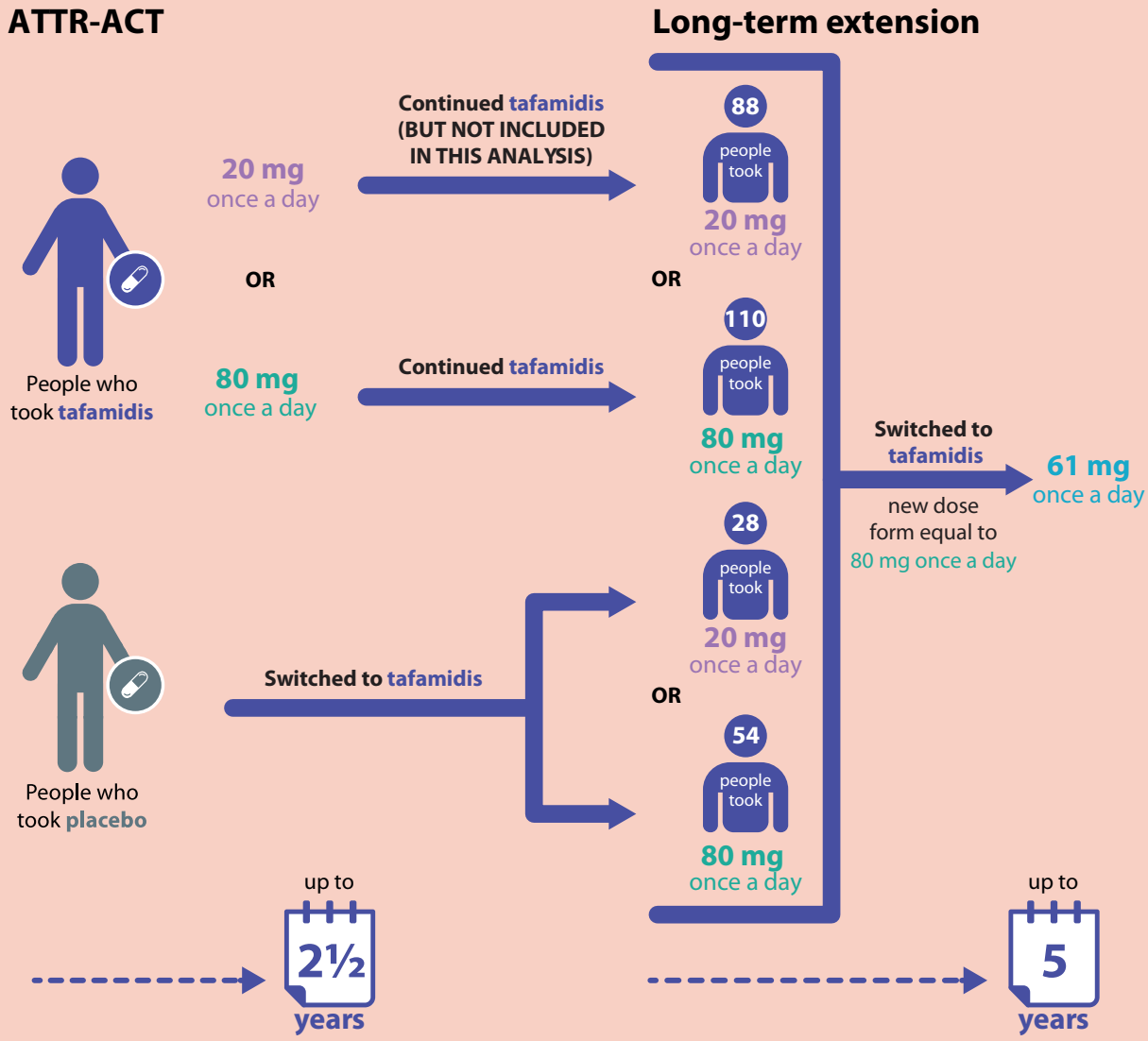
- After completing ATTR-ACT, people could choose to continue treatment in a long-term extension study for up to 5 years.
  - People who took tafamidis in ATTR-ACT continued to take tafamidis in the long-term extension study at the same dose they had previously been taking (20 mg or 80 mg). However, for this analysis, researchers did not include the people who took 20 mg of tafamidis in ATTR-ACT and the extension study.
  - People who took placebo in ATTR-ACT switched to tafamidis in the long-term extension study. They were assigned randomly to take the 20 mg or 80 mg dose.
  - After July 2018, everyone in the long-term extension study switched to a new dose form of tafamidis – 61 mg once daily – for the rest of the extension study. The 61-mg dose form is equal to the 80-mg dose, but it is easier to take because it comes in a single capsule instead of four capsules.
  - In the long-term extension study, researchers looked at the efficacy of tafamidis in people with ATTR-CM over a longer period of time.

1 How many people have taken part in the extension study?

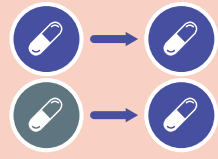


ATTR-ACT long-term extension study registration: https://clinicaltrials.gov; unique identifier number: NCT02791230
*Findings on the race distribution of people who participated in ATTR-ACT can be found at: https://onlinelibrary.wiley.com/doi/full/10.1002/ejhf.2027

2 What dose of tafamidis did people take?



- Researchers wanted to find out how many people died in ATTR-ACT and the long-term extension study. They compared the number of deaths that occurred among people who took:
  - Tafamidis 80 mg in both ATTR-ACT and the long-term extension study; and
  - Placebo in ATTR-ACT and switched to tafamidis 20 mg or 80 mg in the long-term extension study.



- Researchers also wanted to find out if either of the following factors affected people's risk of dying:
  - The type of ATTR-CM they had (wild-type or hereditary).
  - The severity of their heart failure at the start of the study (NYHA class I, II, or III).

What were the results of the extension study?

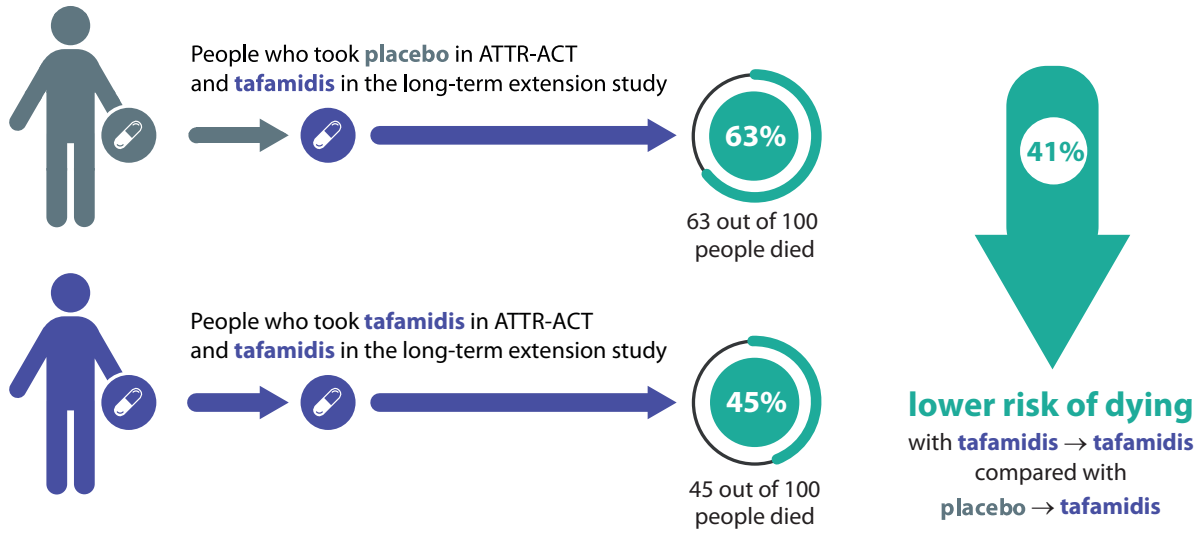
- So far, researchers have looked at findings from people who continued in the extension study for about 2½ years after completing ATTR-ACT. The extension study is expected to end in 2027, so these are interim (not final) results.

1 Did people experience new side effects in the extension study?

- In ATTR-ACT, the safety profile of tafamidis (20 mg or 80 mg) was comparable to that of placebo. The incidence and types of side effects in the extension study were similar to those in ATTR-ACT.
- No new side effects or safety concerns were reported by people who took tafamidis in the long-term extension study.

2 How many people died?

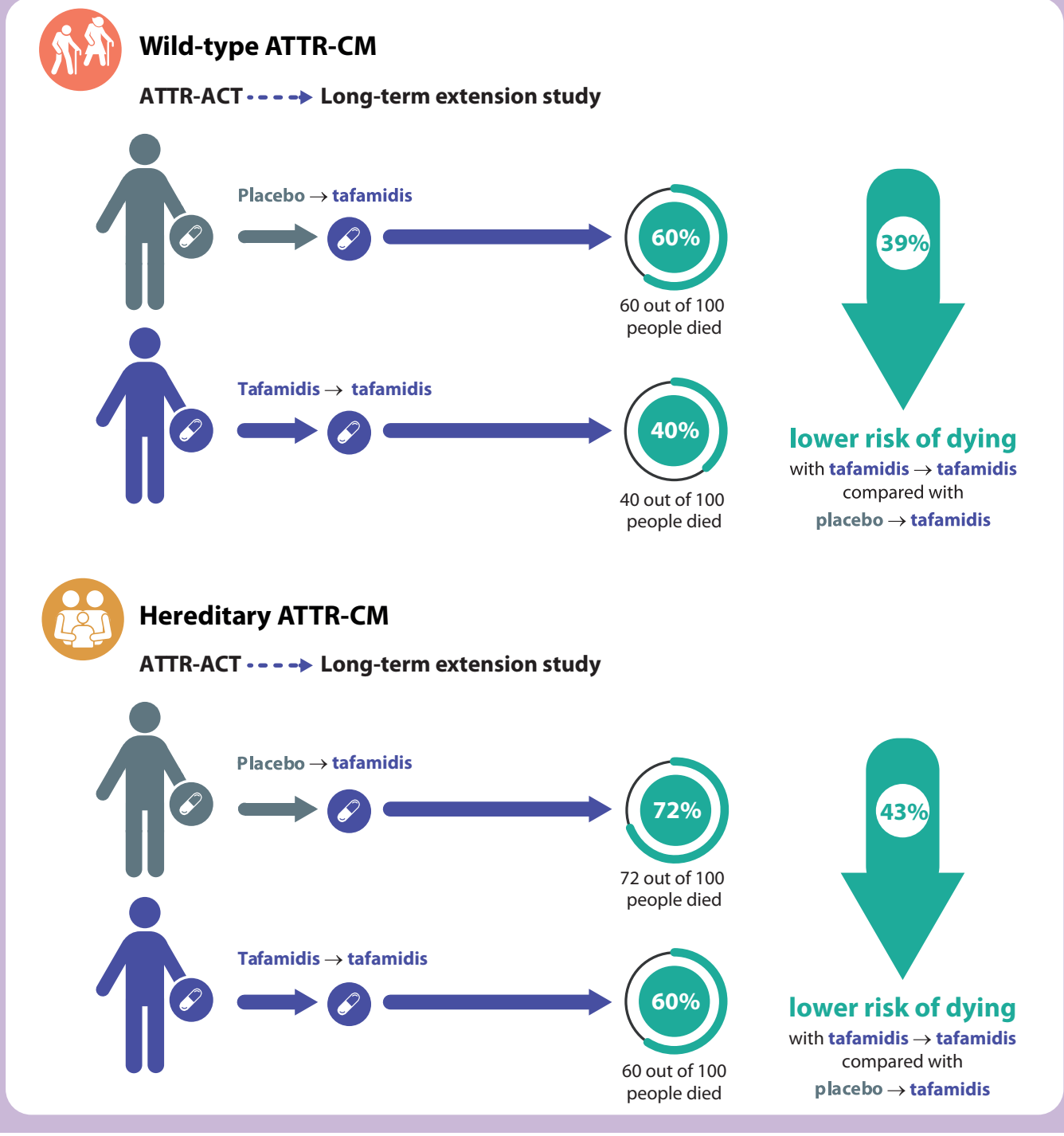
- A smaller percentage of people who remained on tafamidis died than people who took placebo and switched to tafamidis.



People who started taking **tafamidis** in ATTR-ACT had a lower risk of dying than those who initially took **placebo**. This suggests the importance of **early diagnosis and treatment**.

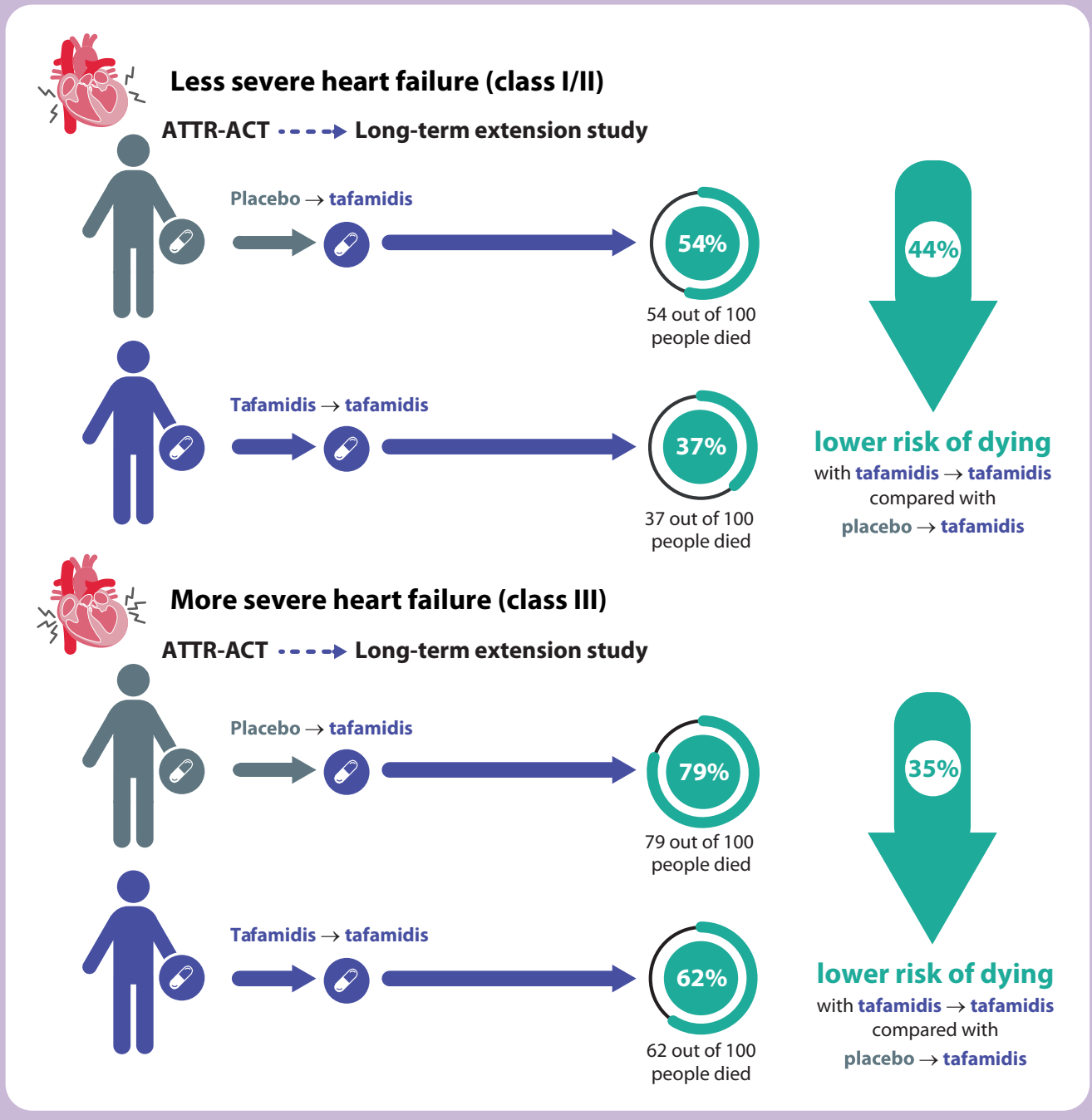
3 Did the type of ATTR-CM affect people's risk of dying?

- Overall, a larger percentage of people with hereditary ATTR-CM died than people with wild-type ATTR-CM.
- Tafamidis treatment reduced people's risk of dying regardless of what type of ATTR-CM they had.
  - The risk of dying was lower in people who took tafamidis continuously than in people who took placebo and switched to tafamidis.



4 Did heart failure severity affect the risk of dying?

- A larger percentage of people with moderate heart failure (class III) died than people with mild heart failure (class I or II).
- Tafamidis treatment reduced people's risk of dying regardless of the severity of their heart failure.
  - People who took tafamidis continuously had a lower risk of dying than people who took placebo and switched to tafamidis.



What were the main conclusions reported by the study authors?

- In ATTR-ACT, tafamidis increased how long people lived with ATTR-CM compared with placebo.
- In the extension study, the risk of dying was lower by 41% in people who took tafamidis earlier and continuously than in people who took placebo and switched to tafamidis.
- The benefits of early, continuous treatment with tafamidis were similar in people with wild-type and hereditary ATTR-CM.
- The benefits of early, continuous treatment with tafamidis were greater in people with ATTR-CM who had mild heart failure than in those with moderate heart failure.
- These results may help improve people's understanding of the long-term benefits of tafamidis treatment for people with ATTR-CM. They may also raise awareness of the need for early diagnosis and early, continuous treatment.

Where can I find more information on ATTR-ACT and the long-term extension study?

You can read more about the long-term extension study at the following website:
https://clinicaltrials.gov/ct2/show/NCT02791230

You can read more about ATTR-ACT at the following websites:
https://clinicaltrials.gov/ct2/show/NCT01994889
https://www.nejm.org/doi/full/10.1056/NEJMoa1805689

Other sources of information

For more information on clinical studies in general, please visit:
https://www.clinicaltrials.gov/ct2/about-studies/learn

For more information on amyloidosis, including patient support groups, please visit:
https://amyloidosis.org (the Amyloidosis Foundation)
https://arci.org (the Amyloidosis Research Consortium)
https://www.amyloidosissupport.org (Amyloidosis Support Groups)
https://mm713.org (Mackenzie's Mission)
https://rarediseases.org (National Organization for Rare Disorders)
https://www.myamyloidosispathfinder.org (My Amyloidosis Pathfinder)

Acknowledgments

Writing support for this summary was provided by Donna McGuire and April Cabang, PhD, at Engage Scientific Solutions and was funded by Pfizer (Pfizer Inc, 235 East 42nd Street, NY, NY 10017, USA; phone: +1 212 733 2323). Authors of the full article were involved in preparing this summary.

Tafamidis is approved to treat the condition under study that is discussed in this summary.

Financial & competing interests disclosure

Full author disclosure information can be found in the original article.