

**Patient
Information**

Amyloidosis and the Heart



Introduction

In some patients with amyloidosis there is a build-up of amyloid deposits in the heart muscle. This may cause no symptoms at all if there is just a small amount of amyloid in the heart. But when amyloid deposits in the heart are large, they can lead to stiffening of the heart muscle so that the heart is unable to pump blood efficiently around the body. Symptoms of heart failure may then appear. This information sheet explains the causes of these symptoms and gives an outline of the recommended treatments, which usually help to provide effective relief.

Which types of amyloidosis affect the heart?

The heart is often affected in:

- AL amyloidosis
- Hereditary amyloidosis:
 - ATTR amyloid deposits consist of 'variant' TTR in patients with a mutation in the TTR gene
 - AApoAI amyloid deposits in patients with a mutation in the apolipoprotein A1 gene
- Wild-type ATTR amyloidosis (formerly known as senile systemic amyloidosis):
 - ATTR amyloid fibrils consist of normal 'wild-type' TTR in patients without a mutation in the TTR gene
 - These types of amyloid deposits are very common in the elderly, but it is not known how frequently they actually cause disease

Heart disease is very rare in AA amyloidosis, only occurring in about two out of every 100 patients.

What are the symptoms of heart failure?



The symptoms of heart failure caused by amyloid affecting the heart may include:

- fatigue
- breathlessness
- swelling of the legs
- loss of appetite
- weight loss
- nausea
- dizziness
- disrupted sleep

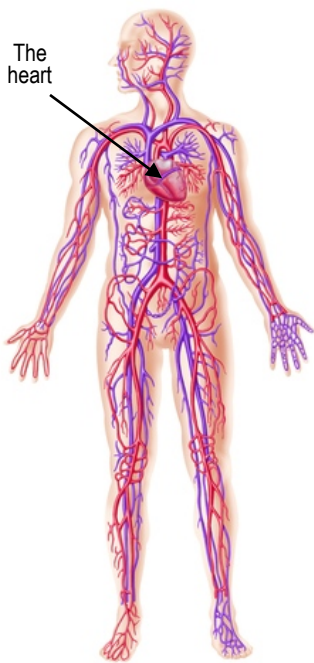
Breathlessness may be worse during exercise or when lying flat at night. Patients may feel more comfortable propped up with several pillows.

Some patients with a small or moderate amount of amyloid in the heart experience no symptoms.

The heart

The healthy heart

The heart is a muscular pump, around the size of a fist, located in the centre left side of the chest. The function of the heart is to maintain a steady supply of blood to the entire body. It does this via a network of blood vessels. These blood vessels are like interconnecting pipes of various sizes. Large blood vessels lead directly from the heart, and branch out into smaller blood vessels which reach every part of the body.



In healthy people, the heart muscle contracts and relaxes between about 60 to 100 times every minute of every day, whether we are awake or asleep. When we are resting the heart rate usually drops and when we exercise or get excited, the heart rate usually rises. The rhythmical contraction and relaxation of the heart muscle leads to a pulse which can be felt in blood vessels close to the surface of the skin, for example at the wrist.

When the heart muscle relaxes, the inner cavities (chambers) of the heart fill up with blood. When the heart muscle contracts, the blood inside the chambers is squeezed out into the blood vessels.

What happens in heart failure?

Most of the usual causes of heart failure, not involving amyloidosis, reduce the ability of the heart muscle to contract and pump out blood efficiently into the blood vessels. This is known as 'systolic' heart failure.

Amyloid deposits in the heart may cause the heart to stiffen, so it is unable to fully relax and fill up with blood. Even though the heart muscle may still be able to contract normally, blood supply to the body is less efficient than usual because of the filling problem. This is known as 'diastolic' heart failure. Diastolic heart failure

may also occur in a number of diseases other than amyloidosis.

When amyloid in the heart causes it to pump less well than usual, there may be reduced blood flow to vital organs. Excess salt and water can accumulate in the body and blood pressure may drop. Patients may then experience the symptoms of heart failure listed in the box on the previous page.

Which tests can help to diagnose amyloid in the heart?



Blood tests: 'cardiac biomarkers'
(NT-proBNP and troponin)

ECG

Echocardiogram

Cardiac MRI scan

Radionuclide imaging (DPD scan)

Heart biopsy

For more details on each of these tests, see the appendix at the end of this information sheet

Treatment of amyloidosis in the heart

Amyloid specific treatment

AL amyloid in the heart

AL amyloidosis is usually treated with chemotherapy. Heart involvement is important for staging and evaluating the prognosis of patients with AL amyloidosis. Doctors take the extent of heart disease into account when making treatment choices. There is sometimes a need for drugs that suppress the abnormal plasma cells rapidly if heart disease appears to be progressing.

Some chemotherapy drugs must be used cautiously when there are AL amyloid deposits in the heart. For example:

- Dexamethasone may cause fluid overload in AL amyloidosis. Diuretics can help to prevent this problem. Treatment co-ordination between haematologists and cardiologists can help to ensure the safest treatment.
- High dose chemotherapy and autologous stem cell transplant is often not suitable for patients with AL amyloid in the heart.

ATTR amyloid in the heart

For 20 years liver transplants have been performed as a treatment for hereditary ATTR amyloidosis. Since all TTR in the blood is produced by the liver, it was hoped that removal of the liver and replacement with a donor liver producing normal, 'wild-type' TTR would be a cure. This has been successful in some patients with the Val30Met mutation. Unfortunately results have been disappointing in patients with other mutations, as the ATTR amyloid deposits in the heart often continue to progress after the liver transplant. The normal, 'wild-type' TTR from the new liver forms amyloid which builds up on top of the existing, 'variant' ATTR amyloid deposits. Liver transplantation is now rarely recommended in the UK as a treatment for hereditary ATTR amyloidosis.

In 2019 two new genetic therapies, patisiran and inotersen, were approved by the regulatory authorities in the EU and the US, and subsequently by NHS England, for treating neuropathy in patients with hereditary ATTR amyloidosis. Since then, the NAC doctors have been able to prescribe these drugs for suitable patients. Patients with wild-type ATTR amyloidosis were not included in these drug trials, but studies focussing on all forms of cardiac ATTR amyloidosis are anticipated in the near future.

Another new drug, tafamidis, is thought to stabilise TTR making it less likely to form amyloid deposits. Tafamidis has been approved for cardiomyopathy caused by ATTR amyloidosis by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It is currently undergoing evaluation by NICE to establish whether it will become available in the NHS.

Other new drugs for ATTR amyloidosis are in various stages of development, both in our Wolfson Drug

Discovery Unit and elsewhere around the world. These drugs offer hope for the future.

Treatment of the symptoms of amyloid heart disease

Many standard medications used for heart failure are not effective for patients with amyloid deposits in the heart, but the following measures can be very helpful:

Fluid balance

Patients with cardiac amyloidosis should limit their fluid intake.

This advice is extremely important, but is often overlooked. The most important principle of treatment for cardiac amyloidosis is strict fluid balance control. Specialist heart failure nurse involvement may be valuable.

When there is cardiac amyloidosis, the heart is often too stiff to pump the blood efficiently. This may lead to fluid build-up, causing leg swelling (oedema) and breathlessness due to fluid in the lungs. This problem is exacerbated if the patient drinks too much fluid.

If there is AL amyloidosis there may also be amyloid deposits in the kidneys. The combination of kidneys that are unable to sufficiently clear the fluid into the urine and a heart that is too stiff to pump efficiently may be problematic. Patients receiving chemotherapy for other conditions (*ie* not AL amyloidosis), or those with AL amyloid that has not affected the heart and/or the kidneys, are told to 'drink plenty' to avoid dehydration. But in AL amyloidosis, this advice may be inappropriate and make matters worse.



The ALchemy (AL amyloidosis chemotherapy) study is a large, on-going, 'real world' study of chemotherapy in AL amyloidosis, started in 2009 and funded by a grant from the charity Myeloma UK. This study has identified fluid overload as the most common serious side effect experienced by patients with AL amyloidosis. It was far more common than any other severe side effects reported. Fluid overload comprised nearly 40% of all the episodes of toxicity. Nearly 1 in 3 of the patients who were hospitalised because of toxicity had fluid overload.

Patients with ATTR amyloidosis in the heart may also experience episodes of worsening symptoms if there is even a small fluid excess. It is preferable to catch and treat heart failure symptoms at an early stage, before they become overwhelming.

Fluid excess can be avoided by careful attention to the 3 Ds:

1. Diet
2. Diuretics
3. Daily weights

1. Diet:

Fluid intake should be *steady* and should usually not exceed *1.5 litres per day*.

Salt intake should be strictly limited. Salt should not be added to food. In addition, this includes attention not just to salt added to the food from the salt pot, but also to food with high salt content such as crisps, bacon, canned meats, sausages, canned soups and smoked fish. It can be very helpful to meet with a dietician for precise and personalised dietary advice.



If salt and fluid intake is too high, the benefits of diuretic drugs can be completely lost.

2. Diuretics:

Doctors may prescribe diuretics (water tablets) which help the body to clear excess salt and water via the urine. Taking these drugs is not a substitute for avoidance of excessive dietary salt and water. If patients consume too much salt and drink too much fluid, the benefits of diuretics may be lost.

Removal of excess fluid from the body leads to reduced ankle swelling and breathlessness. The first diuretic prescribed is often furosemide. Other diuretics such as spironolactone may be added on later to increase the effect. Diuretics lead to increased amounts of urine and should be taken first thing in the morning, sometimes with an additional lunchtime dose. It is important to follow the doctor's advice carefully regarding diuretic dose and the time of day when the tablet should be taken.

3. Daily weights:

Patients should monitor and record their weight daily. Weight should be measured consistently, using the same scales, at the same time of day, usually first thing in the morning after passing urine, just wearing underclothes.

Each litre of excess fluid weighs one kilogram. Several litres of fluid can accumulate in the body without it being very noticeable. But an increase in weight can be an early warning sign of fluid retention.

Variations from week to week or even from day to day of about $\pm 1-2$ kilograms are normal. If there is greater variation in weight, the doctor or nurse treating the patient can recommend appropriate measures. These may include increasing or reducing the diuretic dose. Some patients learn over time how to make appropriate small adjustments to the diuretic dose according to their weight fluctuations.



The aim is to detect and treat any excess fluid, before the patient feels unwell because of the fluid overload.

Support stockings can be helpful for patients with leg oedema (swelling in ankles and lower legs).

Monitor your weight and blood pressure daily. It is helpful if you record them in a chart that you can show your local heart failure team during regular reviews. It is important for your local cardiology/haematology teams to agree to an exact, pre-determined plan for monitoring your fluid balance and adjusting diuretic doses in the event of unexpected fluid retention.

Many patients with cardiac AL amyloidosis may require extra doses of diuretics for a couple of days when they receive dexamethasone during their chemotherapy.

Medications

Many standard heart failure medications reduce the already low blood pressure in patients with cardiac amyloidosis, and can actually worsen the symptoms. Others may cause toxicity in the setting of amyloidosis.

The following drugs should be used with caution:

- calcium channel blockers
- digoxin
- beta blockers
- angiotensin converting enzyme (ACE) inhibitors
- angiotensin receptor blockers

There may be interactions between heart failure drugs and drugs used to treat AL amyloidosis.

If you are concerned, ask your doctor whether any of the medicines you are taking interact. Follow your doctor's advice carefully and take the medicines your doctor prescribes for you.

Under certain circumstances some other treatments may be helpful. For example:

- Alpha agonist drugs such as midodrine may help to maintain blood pressure and allow higher diuretic doses.
- In some cases anticoagulation (warfarin, or one of the new anticoagulant drugs - dabigatran, rivaroxaban, edoxaban or apixaban) may be recommended.
- Pacemakers may be recommended if there is a slow or irregular heart rate.
- An implantable cardioverter-defibrillator may be recommended if there are certain abnormal heart rhythms.

Patients should inform all their doctors of all medications they are taking, including any complementary or

alternative treatments, to avoid any ill effects from drug interactions or side effects.

Exercise

It is believed that limited, light exercise is beneficial for the general well-being of patients with amyloid in the heart. However, it is important to be careful, and to exercise within limits, to avoid exhaustion. If there are symptoms on exercise, patients should not push themselves.

Surgery and anaesthesia

If patients with amyloidosis become ill or require any treatment for a different condition or surgery it is important to inform the treating doctors so that, if necessary, the NAC doctors can be informed, in order to maintain co-ordinated care. It is generally advisable for patients with amyloidosis to avoid undergoing surgery, anaesthesia and other invasive procedures.



If such procedures are necessary, patients should request that the surgeons, anaesthetists and other doctors involved contact the doctors at the National Amyloidosis Centre beforehand, to discuss any special considerations involved. For example, it is very important that great care is taken to monitor and maintain blood pressure and fluid balance throughout such procedures. Care should also be taken because of the tendency of tissues with amyloid in them to bleed and to heal poorly.

Questions or enquiries:



Specialist heart failure nurses are well qualified to guide you with day to day heart failure management. They can often be consulted by telephone, and can help both with heart failure symptoms and with anxiety and stress related to disease. GPs and hospital specialists can also be helpful. The doctors and nurses at the National Amyloidosis Centre can be contacted between 08:00 – 17:30 Monday to Friday at +44 (0)20 7433 2738.

Appendix

Tests that help to diagnose amyloid in the heart

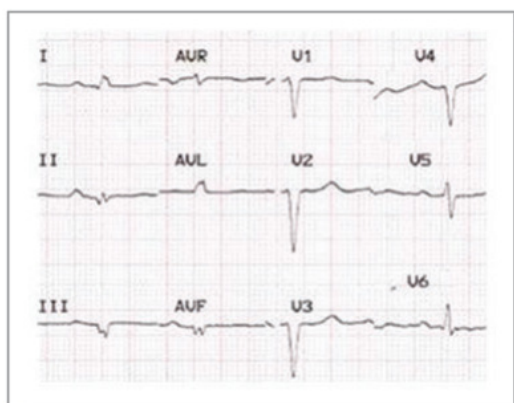
Tests that can help doctors to detect amyloid deposits in the heart include:

Blood tests: cardiac biomarkers

When heart muscle is damaged by amyloid deposits, blood tests may detect raised levels of **NT-proBNP** (N-terminal fragment of brain natriuretic peptide) and **high sensitivity troponin**. These are known as 'cardiac biomarkers'. High levels of these 2 markers in blood tests may be due to heart disease. In AL amyloidosis patients, the results of these blood tests often help to provide doctors with information. This information may be used to stage and evaluate risk at the time of diagnosis and to assess treatment response. The levels of NT-proBNP may fall dramatically within weeks after chemotherapy, even before any change is observed on echocardiography or cardiac MRI.

ECG

The ECG test is a safe, rapid, painless method whereby the electrical impulses controlling the heart's contractions can be detected, measured and represented as a tracing on graph paper. All patients with suspected amyloidosis should have an ECG. The findings can be helpful in making the diagnosis.



Typical ECG of a patient with cardiac amyloidosis
(Image from Banyersad S et al, J Am Heart Assoc, 2012)

Some ECG appearances are suggestive of amyloidosis in the heart, like the ECG shown on this page.

ECG patterns can also provide clues to differentiate between AL and ATTR amyloidosis. Progressive ECG changes may be useful in assessing silent progression of heart disease. After treatment of AL amyloidosis there is usually no change seen in the ECG, but in some cases changes may occur.

Echocardiogram

Echocardiography is an ultrasound test. It is safe and painless and does not involve any exposure to radiation. All patients with suspected amyloidosis should have an echocardiogram. This test is routinely performed when patients visit the National Amyloidosis Centre. When amyloidosis in the heart is advanced, it is usually clearly visible on the echocardiogram. However, the findings may be less clear at the early stages of amyloid heart disease.

Cardiac magnetic resonance (CMR)

CMR is a method whereby a magnetic field and radio waves are used to obtain detailed pictures of the heart. It is safe and painless, and does not involve any exposure to radiation. CMR has been available at the NAC since our new, state of the art CMR unit opened in early 2016.

CMR provides very detailed information on the structure of the heart. In some patients, echocardiography may not be able to determine whether heart wall thickening is due to amyloidosis or to another cause such as high blood pressure (hypertension). In such patients, CMR imaging can help to distinguish between these different causes of heart wall thickening.

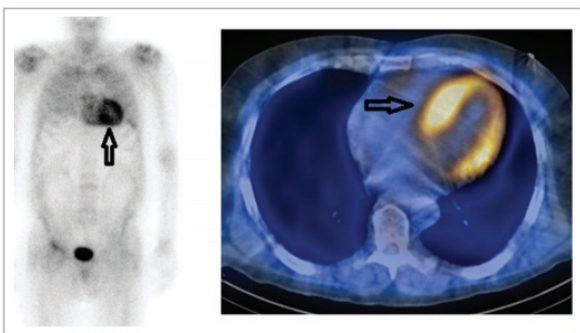
When doctors analyse CMR scans, they can often clearly visualise the amyloid deposits within the heart walls, between the heart cells. It is expected that in the future it may be possible to use CMR to accurately measure the quantity of amyloid within the heart wall. Such measurements could then be repeated to follow the build-up of amyloid deposits and their regression with treatment.

Radionuclide imaging (DPD scan)

SAP scanning does not provide adequate information about body organs that are moving. The heart is in constant motion, so SAP scanning is not of use for assessment of amyloid deposits in the heart.

A different radioactive marker that does home in on amyloid in the heart is called ^{99m}Tc -DPD, or just DPD. Since 2010 hundreds of DPD scans have been performed on patients at the National Amyloidosis Centre with suspected amyloid in the heart.

DPD scans are most useful when the deposits are of ATTR type, and the amount of DPD taken up by the heart correlates with the size of ATTR amyloid deposits. Asymptomatic 'early stage' ATTR amyloid deposits in the heart can sometimes be detected by DPD scans, when other heart tests appear normal. In most patients with amyloidosis, tissue biopsy is required to be certain of amyloidosis type. The NAC doctors recently determined that in some patients without a monoclonal gammopathy, DPD scan findings may be sufficient to diagnose ATTR cardiac amyloidosis without the need for tissue biopsy.



A positive DPD scan for ATTR cardiac amyloidosis
The arrows point at the amyloid deposits in the heart
(Image from Banypersad S et al, J Am Heart Assoc, 2012)

DPD scans are less useful for detecting and evaluating AL amyloid deposits in the heart, as DPD uptake in the heart only occurs in about 1 in 3 patients with AL amyloid in the heart. Even when there is DPD uptake by AL amyloid deposits in the heart, the amount of uptake does not correlate well with the size of deposits.

The DPD scan is made in 3D by a method called single photon emission computerised tomography (SPECT), and is combined with a standard CT scan. The doctors can then assess both the structure of the heart and the extent of amyloid deposits.

DPD scanning and SPECT are safe tests. There may be minor discomfort when the tracer is injected, but the tests are otherwise painless. There is only slight exposure to radiation from the tracer and the CT scan.

Heart biopsy

Heart muscle biopsy involves removal of a small sample of heart muscle which is then examined in the microscope to detect amyloid deposits. It is the 'gold standard' for diagnosing amyloid deposits in the heart. This means that it is the best available test, against which all other tests are measured. This test is performed by cardiologists or cardiothoracic surgeons.

Patients are usually sedated during the biopsy, which usually takes less than an hour. During the procedure, the doctor numbs a small area of skin in the neck or in the upper leg, then inserts a long, narrow tube called a catheter into a blood vessel and threads it through to the heart. X-rays are performed to ensure that the catheter tip is positioned next to the heart wall. Then a grasping device at the end of the catheter is used to remove a tiny sample of heart tissue. The catheter is then withdrawn, bringing the heart tissue with it. The tissue is sent to the laboratory for analysis. The procedure is usually safe and painless, and does not require admission to hospital.

◆ *Funded by a bequest from Laura Lock* ◆

**The Amyloidosis Awareness Programme of the NAC is generously supported by:
Akcea Therapeutics ◆ Alnylam Pharmaceuticals ◆ The Tufton Charitable Trust**