Subject information for participation in medical scientific research

A study on the effect of carotid artery stenting during endovascular treatment of acute ischemic stroke

Official English title: CASES: Stenting a carotid stenosis during endovascular thrombectomy compared to an endovascular thrombectomy with delayed treatment of a carotid stenosis in patients with an acute ischemic stroke caused by a proximal intracranial occlusion.

Introduction

Dear Sir/Madam,

With this information letter we would like to ask you if you would like to participate in medical research. Participation is voluntary. You are receiving this letter because you have suffered an acute ischemic stroke. You have now been informed about this condition by your treating physician. Because it was in your interest to be treated as soon as possible, the medical ethics review committee was asked to postpone your consent to participate in the study until after the treatment. Because the risks of this research are low, the medical ethics review committee has agreed to this. This means that you have already undergone the treatment to be investigated or the standard treatment.
Here you can read what this research study is about, what it means for you, and what the advantages and disadvantages are. It's a lot of information. Would you like to read through the information and decide if you want to participate? If you would like to participate, please fill in the form provided in Annex D.

Ask your questions

You can make your decision with the information you will find in this information letter. In addition, we recommend that you do this:
- Ask questions to the researcher who gave you this information.
- Talk to your partner, family or friends about this research.
- Ask questions to the independent expert. For contact details see Appendix A
- Read the information on www.rijksoverheid.nl/mensenonderzoek.

1. General information

Participants in a medical-scientific study are often referred to as test subjects. Both patients and people who are healthy can be test subjects.

This study was set up by the University Medical Center Groningen (UMCG) and is being done by doctors in various hospitals in Belgium and the Netherlands. The medical ethics review committee

of Erasmus MC Rotterdam has approved this study. General information about the review of research can be found on the website of the Dutch government; www.rijksoverheid.nl/mensenonderzoek.

2. What is the purpose of the study?

The aim of this study is to find out whether immediate stenting of severe carotid artery stenosis during endovascular thrombectomy for acute ischemic stroke is equally effective as deferred treatment of carotid artery stenosis after endovascular thrombectomy.

3. What is the background to the research?

You have been admitted to hospital because you have had an acute ischemic stroke. A ischemic stroke occurs when a blood vessel in the brain is blocked by a clot and a part of the brain therefore does not receive blood and is damaged. The symptoms that can arise from this condition include paralysis, sensory disturbances, language problems and/or partial blindness. To increase the chances of recovery, patients are treated with endovascular treatment via the groin (endovascular thrombectomy) if possible. This is a procedure in which the doctor inserts a very thin tube (catheter) into the artery of your groin and through the blood vessels to remove the clot from the cerebral artery. For this treatment, the sooner the procedure starts, the greater the chance of recovery.
About 1 in 3 treated people are able to function independently after a recovery period of 3 months. In 1 in 5 treated people, the clot is caused by a severe stenosis in the carotid artery. This severe stenosis of the carotid artery increases risk of a new ischemic stroke in the first few weeks. Therefore, people with severe carotid artery stenosis are often operated on within 2 weeks after the ischemic stroke to prevent another ischemic stroke. The carotid artery stenosis can also be relieved immediately during endovascular treatment of an acute ischemic stroke by placing a stent. A stent is a small tube with a mesh structure that can be placed in a blood vessel to correct the stenosis of the carotid artery. The advantages of stenting directly during endovascular treatment is that a patient only has to undergo one procedure and that the risk of a new ischemic stroke is immediately reduced. A possible disadvantage is that people use two blood thinners for a longer period of time after stenting than when there is no stenting. That is why we want to use this research to study whether the immediate stenting of a carotid artery stenosis at the time of endovascular treatment of an acute ischemic stroke works at least as well as delayed treatment of the carotid artery stenosis.

4. How does the research work?

How long does the study take?
Will you participate in the study? Then it takes about 3 months in total, from treatment to final (telephone) check-up.

Step 1: Your eligibility for the study
In order to participate in this study, the investigator checked whether you are suitable. The criteria are described below;

- Age above 18 years

- Degree of neurological complaints
- On imaging, a clot that occludes one of the cerebral arteries
- A severe stenosis or occlusion in the carotid artery on the same side as the clot
- No cerebral hemorrhage on imaging (within 6 weeks)
- No recent ischemic stroke or brain trauma (within 6 weeks)
- No recent other gastrointestinal or bladder bleeding (within 6 weeks)
- No allergy to anticoagulant medication
- No longer-standing neurological deficit that interferes with daily activity
- No pregnancy
- (Deferred) written consent for participation

Justification of deferred consent

First, the treatment of ischemic stroke is carried out as soon as possible. For every hour of delay, the chance of recovery and being able to carry out daily activities independently (ADL) decreases by 6%. In previous acute stroke studies, it has been found that waiting for treatment consent led to an (unacceptable) delay in the start of treatment.

Secondly, during the acute phase of a ischemic stroke, a patient is often unable to make an informed decision whether or not to participate in a study, for example due to disabilities such as language disorders, inability to communicate or reduced insight into the disease. Obtaining consent from the patient's proxy may also lead to unacceptable delays in acute treatment.

In summary, due to the emergency situation and the potential lack of decision-making ability, the process cannot be carried out without deferred consent. This approach has been successfully used in recent studies on ischemic strokes in the Netherlands.

Step 2: the treatment

Because the treatment had to take place urgently, you have already been assigned to one of the following two groups.

Group 1: has immediately undergone a stenting of the carotid artery at the time of endovascular treatment for the acute ischemic stroke.

Group 2: has not undergone carotid artery stenting at the time of endovascular treatment for the acute ischemic stroke (control group, standard of care).

The division into treatment groups and undergoing the treatment was done with the agreement of a medical ethics committee prior to requesting permission. It is important to inform yourself regarding the details of the research. Since it is important to treat ischemic strokes as soon as possible in order to save as much brain tissue as possible, this is not possible prior to treatment.

In order to keep the distribution over both groups as equal as possible, it has been determined by lottery which group you have ended up in. More information about drawing lots can be found on the website of the Dutch government.

If you have been placed in group 1, a stent will have been placed in your carotid artery at the time of endovascular treatment. This treatment means that you are transported to a treatment room almost immediately after the scan that has been made of your head. Once in the treatment room, a catheter was inserted into the artery of your groin under local anesthesia, a sedation or general anesthesia. Under X-ray, this catheter is advanced to the blocked blood vessel in your head. There, an attempt was made to remove the clot by means of catheter techniques (with a removable stent and/or a small suction tube). The procedure took about 1 hour. During this procedure, the carotid artery stenosis was also treated at the same time with a permanent stent that was also placed through the blood vessels in your carotid artery via catheters.
If you have been drawn for group 2, the control group, then you have undergone the endovascular treatment without the placement of a stent in the carotid artery. However, it is possible that the stenosis has been corrected with angioplasty (carefully inflating a balloon in the stenosis) to be able to get past this stenosis to remove the blood clot in the brain. However, angioplasty alone does not give sufficient results in the long term. This means that if you recover well in the coming weeks, there may be additional surgery to remove the carotid artery stenosis.

Step 3: Surveys and measurements
During the hospitalization, the following measurements/tests/treatments have already taken place:

- Physical examination in the emergency department before the endovascular treatment and immediately after the endovascular treatment at the stroke unit by the treating physician.
- CT scan with and without contrast in the emergency department
- Endovascular treatment with or without carotid artery stent placement

During the hospitalization, the following measurements/tests may still take place:

- We will do a CT scan with and without contrast of your neck and brain about 24 hours after the treatment
- We will perform a physical examination approximately 5-7 days after treatment or before discharge from the hospital (if discharge is earlier than 5-7 days).

After discharge from the hospital, you will be called once by the study team. This phone call will take place approximately 3 months after the treatment. You will then be asked questions about your state of health. This appointment will take about 15 to 30 minutes and will be scheduled with a member of the research team from the UMCG. There will also be an ultrasound examination of the carotid artery after 3 months. Finally, you will receive a questionnaire at home with questions about how you experience your own health, whether you have been able to resume your work and whether you have been treated by other doctors.

What is different from regular care?

In Group 1, the carotid artery is treated earlier by means of stent placement during acute endovascular treatment. Group 2 will receive standard treatment, in which the carotid artery will be treated later by surgery, a stent, or medication alone.
Some of the examinations are part of the usual care. Additional examinations in the context of this study are the CT scan with and without contrast approximately 24 hours after the endovascular treatment and an ultrasound examination of the carotid artery after 90 days. A schematic overview of these examinations can be found in Appendix C.

5. What agreements do we make with you?

We want the research to go well. That is why we make the following agreements with you:

- You will not participate in any other medical-scientific study during this study.
- You come to every appointment.
- You contact the investigator in these situations:
  - If you are admitted to a hospital or treated.
  - If you suddenly develop health problems
  - If you no longer wish to participate in the study.
  - Your phone number, address or e-mail address has changed.

6. What side effects, adverse effects or discomforts may you experience?

It is known that blood thinners that are necessary for the placement of a stent increase the risk of bleeding in patients with ischemic stroke. Not stenting the carotid artery stenosis immediately during endovascular treatment, the standard treatment, increases the risk of a new ischemic stroke. In addition, you may still need surgery on your carotid artery in the coming weeks.

Radiation exposure

During a CT scan, we use X-rays. The total radiation exposure in this study is 4 mSv in the CT scan with and without contrast. By way of comparison: the background radiation that every inhabitant in the Netherlands receives is ~2.5 mSv per year. The radiation used during the examination can lead to damage to your health. However, this risk is very small.

7. What are the advantages and disadvantages of participating in the study?

Participating in the study can have advantages and disadvantages. We list them below. Talk about this with others and if you have any questions, please contact the investigator or the independent physician (contact details can be found in Appendix A).
It is important that you have a good understanding of the potential benefits and drawbacks. Stenting the carotid artery directly can have a positive effect on your recovery after the ischemic stroke and reduce the risk of a new ischemic stroke, but that is not certain. No study has yet been done to draw firm conclusions about the effect of the treatment. However, based

on previous studies, patients who have undergone carotid artery stenting during endovascular treatment seem to have the same treatment effect as patients who have not undergone stenting. Furthermore, we think that fewer new ischemic strokes would occur in the stenting group. Finally, if you recover well, you will no longer need surgery on your carotid artery in the coming weeks.

Disadvantages of participating in the study can be:

- Possible adverse effects/discomforts of the examinations and scans in the study.
- A possibly slightly higher chance of cerebral hemorrhage occurring for patients in group 1.
- A possibly slightly higher chance of a new ischemic stroke for patients in group 2.
- Any additional surgery on the carotid artery in group 2.

Don't want to participate?
You decide whether you want to participate in the study. Participation is voluntary.
If you do not want to participate, you will continue to be treated for your ischemic stroke in the usual way.
If you do participate, you can always change your mind and still stop, even during the study. You will then be treated in the usual way. You don't have to say why you're quitting. However, you must report this immediately to the investigator.
If there is new information about the study that is important to you, the investigator will let you know. You will then be asked if you will continue to participate.

8. When does the study end?

The investigator will let you know if there is new information about the study that is important to you. The researcher will then ask you whether you will continue to participate.

Your participation in the study will stop if;

- the phone conversation with the investigator took place after approximately 3 months;
- you choose to stop;
- the UMCG, the government or the assessing medical ethics review committee decides to stop the research.

The entire study is over when all participants are finished.

What happens if you stop the study?
The data collected up to that point will only be used if you do not object to its use in an encrypted form that cannot be directly traced back to you. If you do object, the collected data will be destroyed. You can indicate this on the information form "Use clinical data in case of no consent", attached to this letter. Your treating physician will be able to tell you more about the treatment options available and the pros and cons of them.

9. What happens after the study?

Will you get the results of the study?

After processing all the data, the investigator will inform you about the main outcomes of the study. This will be done no later than 4 years after your participation.

10. What do we do with your data?

Will you participate in the study? Then you also consent to the collection, use and storage of your data.

What data do we store?
We store this data:
-Your name
- your gender
- your address
- your date of birth
- information about your health, neurological complaints and degree of disability
- imaging of the brain and blood vessels
- Information from the ambulance service about the transport to the hospital.

What body material do we store?
No bodily material is stored.

Why do we collect, use and store your data?
We collect, use and store your data in order to be able to answer the questions of this study. And to be able to publish the results. Data may be used by the sponsor and companies that assist the sponsor in conducting the study and analyzing research data. We also need this data to be able to market the treatment under investigation.

How do we protect your privacy?
To protect your privacy, we provide your data with a code. This code is placed on ally our data. We keep the key to the code in a secure place in the hospital. When we process your data, we only use that code at all times. Also, in reports and publications about the research, no one can retrace that it was about you.

Who can see your data?

However, some people will be able to see your name and other personal information without a code. This can be data collected specifically for this study, but also data from your medical file.
These are people who check whether the researchers are conducting the research properly and reliably. These people can access your data:

- The coordinating research team.
- Members of the committee that monitors the security of the investigation.
- An independent auditor.
- National and international regulatory authorities, such as the Food and Drug Administration (FDA).

These people will keep your information confidential. We ask you to give permission for access by these persons. The Health and Youth Care Inspectorate (Inspectie Gezondheid & Jeugd) can view your data without your permission.

How long do we keep your data?
We keep your data in the hospital for 15 years.

What happens in the event of unexpected discoveries?
During the investigation, we may happen to find something that is not directly relevant to the study, but is important to your health or to the health of your family members. The investigator will then contact your general practitioner or specialist. You will then discuss with your GP or specialist what needs to be done. The costs of this are covered by your own health insurance. With the form, you give permission for your GP or specialist to be informed.

Can you revoke your consent to the use of your data?
You can revoke your consent to the use of your data at any time. Please inform the researcher. This applies to use in this study and to use in other studies. But beware: do you withdraw your consent, and have researchers already collected data for a study? In that case, they are still allowed to use this data.

Would you like to know more about your privacy?

- Would you like to know more about your rights in the processing of personal data? Then take a look at www.autoriteitpersoonsgegevens.nl.
- Do you have questions about your rights? Or do you have a complaint about the processing of your personal data? Please contact the person responsible for processing your personal data. For your research, that is:
  - See Appendix A for contact details, and website.
- If you have any complaints about the processing of your personal data, we recommend that you first discuss them with the investigation team. You can also go to the Data Protection Officer of the hospital. Or you can file a complaint with the Dutch Data Protection Authority.

Where can you find more information about the study?
You can find more information about the study on the following website(s).

- ISRCTN registry, www.isrctn.com/ You can find the survey by searching for 'carotid artery stent' or by searching by number: 14956654;
- CONTRAST consortium; www.contrast-consortium.nl/cases/

After the study, the website may show a summary of the results of this study.

11. Will you be compensated if you participate in the study?

Participating in the study does not cost you anything. You will not be paid for participating in this study. However, you will be reimbursed for any additional travel costs.

12. Are you insured during the examination?

Insurance has been taken out for everyone who participates in this study. The insurance covers damage caused by the examinations. Not all damage is covered. You can find more information about the insurance in Appendix B. It will also tell you to whom you can report damage.

13. We inform your General Practitioner (GP)

We will always send your GP a letter to let you know that you are participating in the study. This is for your own safety. If you do not approve of this, you will not be able to participate in this study.

Even if you decide not to participate in the study, we will inform your GP about the treatment you may have received as part of the study.

14. Do you have any questions?

If you have any questions about the study, please contact the research team. Do you want advice from someone who has no interest in it? Then go to the independent expert, for contact details see Appendix A. He knows a lot about the investigation but does not play a role in or cooperate with this research.

Do you have a complaint? Discuss this with the researcher or doctor who is treating you. Would you rather not do this? Then go to the complaints officer/complaints committee. Appendix A tells you where to find them.

15. How do you give permission for the study?

You can first think about this research calmly. After that, you tell the researcher whether you understand the information and whether or not you want to participate. Would you like to participate? Then you fill in the consent form that you will find with this information letter. You and the investigator will both receive a signed version of this consent statement.

Thank you for your time!

Appendices to this information

A. Contact Details
B. Information about the insurance
C. Schedule of investigative actions
D. Subject Consent Form
E. Use of clinical data in case of non-consent

Appendix A: contact details for Erasmus MC

Local Principal Investigators:
Prof. Dr. D.W.J. Dippel, neurologist
Drs. P.J. van Doormaal, interventional radiologist
Reachable via: 010 704 0 704

Independent Physician:
Dr. B. Jacobs, neurologist UMC Groningen
Can be reached via: 050 - 3612400

Complaints:
If you are not satisfied with the examination or treatment, you can contact the independent complaints office/complaints officer of Erasmus MC.
A Digital Complaint Form is available on the Erasmus MC website via
https://www.erasmusmc.nl/nl-nl/patientenzorg/klachtenopvang-en-klachtenbemiddeling
After completing the form, the form is automatically sent to the complaints officer.
If you are unable to complete the digital complaint form, you can also send your complaint by post: Erasmus MC, Secretariat for the Reception of Complaints (GK-745), Antwoordnummer 55, 3000 WB Rotterdam.
In the letter, please include your name, patient number (if applicable), name of the study, and contact details. Upon receipt of the letter, the complaints officer will contact you.

Data Protection Officer of the institution:
The Data Protection Officer of Erasmus MC can be reached via the
Secretariat of the Legal Affairs Department.
Email: functionaris.gegevensbescherming@erasmusmc.nl
Tel: 010-703 4986

For more information about your rights:
For more information or if you have any questions about your rights, please contact the Data Protection Officer or the Dutch Data Protection Authority.

Appendix B: Insurance Information

The UMCG has taken out insurance for everyone who participates in the study. The insurance will pay for the damage you have as a result of participating in the study. This concerns damage that you receive during the study, or within 4 years after the end of your participation in the study. You must report damage to the insurer within 4 years.

Have you suffered any damage as a result of the investigation? Then report this to this insurer:

The insurer of the study is: Name of insurer: Centramed Address: P.O. Box 7374, 2701 AJ Zoetermeer, The Netherlands Telephone number: 070 301 7070 Email: ... (Policy number: 624.529.102

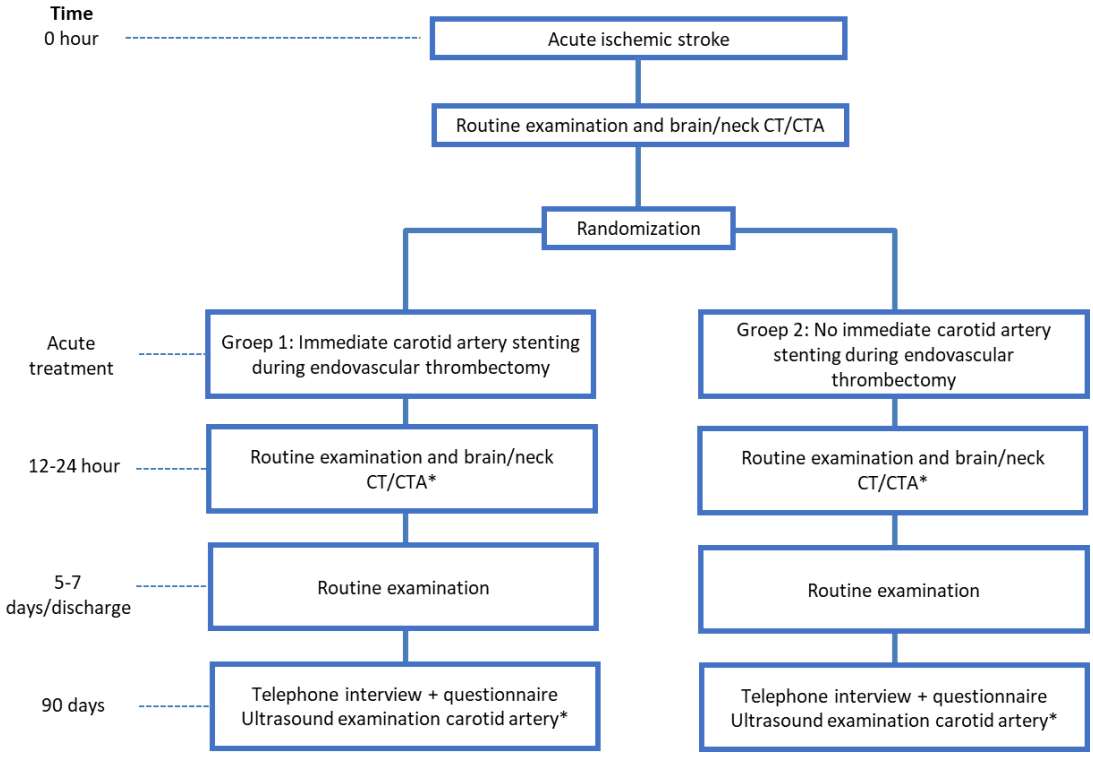
The insurance pays a maximum *of €650,000 per person* and €5,000,000 for the entire study and *€7,500,000* per year for all studies of the same client.

Please note that the insurance does not cover the following damages:

- Damage due to a risk about which we have provided you with information in this letter. But this does not apply if the risk turned out to be greater than we thought beforehand. Or if the risk was very unlikely.
- Damage to your health that would have occurred even if you had not participated in the study.
- Damage caused by the fact that you did not follow directions or instructions or did not follow them properly.
- Damage to the health of your children or grandchildren.
- Damage caused by a treatment method that already exists. Or by researching a treatment method that already exists.

These provisions are set out in the 'Decree on Compulsory Insurance for Medical Research Involving Human Subjects 2015'. This decision is published in the Government Bench of Laws (https://wetten.overheid.nl).

Appendix C: Schedule of investigative examinations



A schematic representation of the examinations and treatments during participation in the CASES study

* means that these examinations are extra on top of the regular care.

Appendix D –Subject Consent Form

A study on the effect of stenting carotid stenosis during endovascular treatment of acute ischemic stroke.

- I have read the information letter. I was also able to ask questions. My questions have been adequately answered. I had enough time to decide whether to participate in the study.
- I know that participation is voluntary. I also know that I can decide at any time not to participate or to stop the study. I do not need to give a reason for that.
- I give permission for my GP to be informed that I am participating in this study. The GP is also informed of unexpected findings.
- I give permission for some people to view my data. These persons are listed in this information letter.
- I give permission for information to be requested from the ambulance service about the transport to the hospital.
- I consent to the collection and use of my data, in the manner and for the purposes stated in the information letter.
- I give permission that the research data from this study may be used by the funder of this study (BeNeFIT call, being KCE in Belgium and ZonMw in the Netherlands) or similar public health institutions in Europe for additional analyses such as determining which treatment is the most cost-effective. The investigators who carry out these analyses will not have access to your identifying data and are bound by professional secrecy.
- I consent to my study data being kept at the study site for at least 15 years after this study. This could possibly be used for new research.
- I
  - □ **give**
  - ○ **Do not give** permission to approach me again after this examination for a follow-up examination.

Subject's name:
Signature: Date: / / Time: :

I declare that I have fully informed this subject about the said study.

If information becomes known during the study that could influence the consent of the subject, I will inform him/her in a timely manner.

Name of investigator (or his/her representative):
Function: □ Attending physician
□ Researcher

Signature: Date: / /

The subject will be provided with a full information letter, along with a copy of the signed consent form.

Appendix E: Use of Clinical Data in the Event of Non-Consent

A study on the effect of stenting carotid stenosis during endovascular treatment of acute ischemic stroke.

- I have read the information letter. I was also able to ask questions. My questions have been adequately answered. I had enough time to decide whether to participate in the study.
- I **do** not consent to participate in the study, no blood samples, examinations, and interviews may be performed that are not necessary for my treatment.
- I □ **Do**
  - **Do not** object to the use of my already collected research data in coded (not directly traceable) form.
- I □ **Do**
  - **Do not** object to the use of the yet to be recorded clinical data from the first 3 months after treatment that will be obtained in the context of regular care, in coded (not directly traceable to the person) form.

Subject's name:
Signature: Date: / /
Time:

I declare that I have fully informed this subject about the said study.
If information becomes known during the study that could influence the consent of the subject, I will inform him/her in a timely manner.

Name of investigator (or his/her representative):
Investigator Position: □ Attending physician
□ Researcher

Signature: Date: / /

The subject will be provided with a full information letter, along with a copy of the signed consent form.