

# **Information for first-degree relatives when participating in a scientific research project**

The prevalence of the Bicuspid Aortic Valve and Associated Abnormalities of New-borns and First-degree Relatives

We would like to invite you to participate in the scientific research project “The Prevalence of the Bicuspid Aortic Valve and Associated Abnormalities of New-borns and First-degree Relatives”. The study is carried out by medical doctors at The Department of Cardiology at Rigshospitalet and Herlev Hospital.

Participation is voluntary and even if you choose to participate you can always withdraw your consent of participation. Should you choose not to participate in the project it will not be of any consequences to your further medical treatments.

Before you decide if you would like to participate in the study you should be fully aware of how we do the examinations and why we do them. Which is why we ask you to read this information thoroughly.

You should also read the information for participation in research projects:

“Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt”. However, this is only available in Danish.

## **Background knowledge and purpose of the study**

### **Purpose**

The purpose of the study is 1) to investigate the occurrence of the bicuspid aortic valve of newborns and their first-degree relatives, and of first-degree relatives of healthy newborns (the control group), 2) to map inheritance and hereditary factors for the bicuspid aortic valve and associated abnormalities, and 3) to investigate the benefits of family screening.

### **The Bicuspid Aortic Valve**

The aortic valve is placed between the left heart chamber and the main artery, aorta. The aortic valve functions as a “one-way vent”, which means that the aortic valve ensures that the blood doesn’t run back to the heart when it has been pumped into aorta. Normally the aortic valve has 3 leaflets called a tricuspid aortic valve, and they open and close during a heart cycle. Some people only have a 2-leaflet aortic valve, which is called a bicuspid aortic valve. The bicuspid aortic valve is expected at approximately 0,5-2% of all newborns. However, the diagnosis of a bicuspid aortic valve is very hard to make through

examinations with a stethoscope, which means some patients will only be diagnosed later in life – either as a random discovery or as a patient who has symptoms of the illness.

It has been brought to attention that the bicuspid aortic valve has been associated with more complications that can arise in adulthood, including narrowing and/or leaking of the aortic valve, as well as inflammation of the aortic valve. There could be an enlargement of aorta which can cause an enhanced risk of tearing or rupturing if not treated in time.

Children that are diagnosed with a bicuspid aortic valve are monitored with a rare five-year gap since the aortic valve initially is well-functioning during childhood and adolescence. Now all patients with a bicuspid aortic valve are offered a lifelong medical follow-up with an ultra sound scan of the heart (echocardiography) and possibly an MRI scan of aorta.

In recent years it has been brought to attention that the bicuspid aortic valve is hereditary. Furthermore, it has also been brought to attention that associated abnormalities, i.e. an enlarged aorta, changed shape and circulation of aorta in the chest, as well as changed flow conditions in aorta are also particularly found in families with a diagnosis of the bicuspid aortic valve without it necessarily being a bicuspid aortic valve. Present medical guidance recommends family screening, including genetic testing, when bicuspid aortic valve is diagnosed.

### **Why is a control group important?**

To understand the conditions concerning the bicuspid aortic valve is important that we also screen families where a bicuspid aortic valve has NOT been found at a heart scan in Copenhagen Baby Heart. These families will be the control group in the study. The control group is necessary to compare the screening results of the control group to the families of the newborn with a bicuspid aortic valve. Which is why you can contribute with important knowledge to this research study if you are a family member of a newborn without a bicuspid aortic valve.

## **Procedure**

### **Newborns and first-degree relatives**

All newborns that are diagnosed with a bicuspid aortic valve at a heart scan in Copenhagen Baby Heart, as well as their first-degree relatives, will be offered a family screening in this sub study. A control group consisting of healthy newborns and their first-degree relatives will also be offered participation in this sub study. Please be aware that if you agree to participate in the screening you automatically agree to receive information about other medical findings at the examinations, also if they are abnormal.

### **The examinations**

If you want to participate there will be the following examinations:

- *Health examination.* We will ask questions about your health and hereditary illnesses in your family. You will have your height, weight, pulse and blood pressure measured, and we will listen to your lung and heart using a stethoscope.
- *Ultrasound scan of the heart outside the rib cage (transthoracic echocardiography).* By this examination we can see how your heart pumps and relaxes, measure the thickness of the heart walls, see how the heart valves function, see if the heart valve is tricuspid or bicuspid, and check the first part of the main artery, aorta.
- *Ultrasound scan of the heart from the throat transesophageal echocardiography).* Using this examination, it will be easier to examine the heart valves, including if the aortic valve is tricuspid or bicuspid.
- *Heart diagram (electrocardiogram, ECG).* We check your ECG for signs of heart rhythm interruptions and heart muscle thickening.
- *Blood samples.* Blood samples are used for genetic evaluation for the bicuspid aortic valve and associated abnormalities. The blood sample and the genetic analysis is NOT a part of the examination of the control group (healthy newborns and their first-degree relatives).
- *Magnetic scan of aorta (MRI).* This is used to show us how your aorta acts in the chest and how the blood runs through aorta (we are looking at the flow conditions). Selected participants will be invited to an MRI.

Patients who have metal parts in their bodies are in some cases not able to have an MRI scan and will not be offered one.

During the study we will collect relevant information from your medical journal, if you have any records. It concerns information about hereditary illnesses, chronic disease and course of pregnancy.

You should also know that with your consent you give the responsible doctors the opportunity to use the information from your medical journals to make quality control of the project. And your consent also includes access to distributing and using necessary information about the health conditions of the test person, other private conditions, and other confidential information as part of the relevant authorities' legal control of the study.

### **Appointments**

You will be invited to a preliminary examination with a regular medical examination, the ECG, transthoracic ultrasound scan of the heart, as well as blood samples for genetic evaluation of the bicuspid aortic valve and associated abnormalities. We are also going to ask you if you would like to have a transesophageal echocardiography to give us the opportunity to check the aortic valve more thoroughly. It takes about 1,5-2 hours.

Blood samples and the genetic evaluation is NOT a part of the examination of the control group (healthy newborns and their first-degree relatives).

Some participants will we selected to receive an invitation to another examination with an MRI scan of aorta. This will last approximately 45 minutes.

### **Usefulness of the project and the examinations**

This study gives us an opportunity to have an account of the frequency of the bicuspid aortic valve and other associated heart abnormalities for newborns as well as first-degree relatives. The purpose of the family study is to map the significance of hereditary factors, as well as examining the benefits of a screening in order to ensure the right medical follow up and treatment for family members that could be affected. Children and relatives that are

diagnosed with a bicuspid aortic valve will be offered a follow up according to existing guidelines and not connected to the project. Therefore, this research project will be useful for you and your family, and also useful for other families with cases of a bicuspid aortic valve. It will also be important for future research.

### **Risks and discomfort at the examinations**

Please be aware that if you agree to participate in the study you also agree to receive information about other conditions we might find at the medical examinations – also if they turn out to be irregular. If you are examined you will receive information about your heart – i.e. how it pumps and relaxes, thickness of the heart walls, the main artery, how the heart valves function and look – also if anything happens to be abnormal.

If you are diagnosed with a heart disease you will be offered a clinical follow up according to existing guidelines and not connected to the project.

In connection to these examinations you could have a diagnosis of a heart-condition or a disease which is either without any significance or normally doesn't require any follow ups or perhaps treatment later in life. In these cases, the results of the scan could cause unnecessary concern.

But there is also a chance you could be diagnosed with a heart disease and receive treatment before unnecessary complications occurs.

### **Transthoracic echocardiography (TEE)**

The ultra sound examination of the heart with a probe placed outside the rib cage. There are no risks, side effects or pain. There could be some discomfort from lying still on your left side during the examination. It takes approximately 20-30 minutes.

### **Transesophageal Echocardiography (TEE)**

The ultrasound examination of the heart, from inside the esophagus in the throat where the probe is placed close to the heart, provides a better view of the heart and enhances the picture quality of the heart structures. This examination is especially relevant when the

heart valves have to be checked more closely for i.e. constrictions, leaks, as well as morphology, when a transthoracic echocardiography isn't sufficient. Patients going to a TEE examination shouldn't eat 6 hours before the examination or drink anything 2 hours before. A sedative will be dispensed through a drip needle in a vein on top of the hand so the patient experiences less discomfort making the examination easier. A local anesthesia will be given in the mouth before the ultra sound probe is inserted through the mouth and into the esophagus. The insertion of the ultra sound probe can cause slight discomfort and gagging reflex, but as soon as the probe is placed correctly this will go away. The sedative and the local anesthesia make the examination less uncomfortable and numbs the gagging reflexes. The patient is fully able to breathe during the examination which takes about 15 minutes. In rare cases (<0,5%) you can have an irregular heart rhythm during the examination or be very influenced by the sedative. This will be treated immediately in these cases. The patient can be slightly sore in the throat 1-2 days after the examination.

### **MRI Scan**

The MRI scan is without the use of contrast dye fluid. For people with metal implants the MRI scan will in some case be withdrawn, and you will be excluded from the MRI part of the study if you have such a metal implant.

Discomfort can occur from lying still on your back for the duration of the examination, approximately 45 minutes.

### **Blood samples**

A small bleeding can occur from the insertion spot. The infection risk is rare. The amount of drawn blood per family member is up to 12 ml and insignificant. Blood tests and genetic evaluation is not part of the screening of the control group (healthy newborns and their first-degree relatives). The excess blood not used for this study is discarded immediately.

### **Genetic screening**

If we detect bicuspid aortic valve in your family the genetic screening will help us explain which genetic change is caused by this. In many cases we will not be able to find the genetic change that caused bicuspid aortic valve with the present knowledge, but from systematic examination of a small number of genes that are related to abnormality in the

heart valve and the main artery we expect to increase our knowledge of the significance of genetic change for the development of the bicuspid aortic valve.

You can have a genetic change that hasn't caused a bicuspid aortic valve. In this case we will offer a future follow up to check if changes of the aortic valve or other heart abnormalities will develop in the future. For some patients this knowledge can be uncomfortable, which we will provide guidance for accordingly. Even if it is just a small number of genes that are examined at this genetic screening, we will also be able to find genetic changes that could be linked to the development of other diseases. According to this, it is very important that you - **ALREADY BEFORE THE BLOOD SAMPLE IS TAKEN** - consider if you would like to be informed of so-called "random" genetic discoveries.

### **Practicalities**

Participation in this study means that you will be invited to 1-2 appointments depending on which examinations you will have.

### **Withdrawal and discontinuation of the study**

You can at all times leave the study without giving any reasons. The study will only be discontinued before time if scientific evidence appears that clearly makes the results of this study redundant.

### **Authorisations**

The project has been approved by the health research ethics committee for The Capital Region of Denmark (H-17029641) as well as The Danish Data Protection Agency.

### **Results**

When the project is completed, and all the results are ready, you will receive – if you want to – the written information about the project results.



### **If you don't want to participate**

If you choose not to participate in the project, it will not be of any influence of your future treatments.

### **Heads of the project and clinical responsibilities**

Professor, dr.med. Henning Bundgaard  
Department of Cardiology, Rigshospitalet

Professor, dr.med. Kasper Iversen  
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### **Contact person**

If you have other questions before, during or after the project, you are welcome to contact medical doctor and PhD-student Jakob Boesgaard Norsk, phone number: 3868 6530/3868 6405 or mail: jakob.boesgaard.norsk@regionh.dk

### **Economy**

This sub study has partly been financed by a private Danish trust fund situated in Lichtenstein (Candys Foundation) – total amount is 1.287.600 DKK. We currently apply for funding from other foundations. If we are granted other funding, we will inform the Danish Health Research Ethics Committees and update the funding information.

The doctors involved have no economic interests in the project:

We don't provide economic compensation for transportation to clinical follow ups or loss of working hours.

We hope that this information thoroughly covers what is to know about participation of this study, and that you feel ready to make a decision about participation or not. Otherwise you are welcome to contact doctor and Ph.D.-student Jakob Boesgaard Norsk by phone: 3868 6530 / 3868 6405 or by e-mail: [Jakob.boesgaard.norsk@regionh.dk](mailto:Jakob.boesgaard.norsk@regionh.dk)

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