PATIENT INFORMATION

ORIGINAL STUDY TITLE: "Dapagliflozin after Transcatheter Aortic Valve Implantation"

SPANISH STUDY TITLE: "Dapagliflozin after implantation of percutaneous aortic valve prosthesis"

PROMOTOR: Geriatric Cardiology Section, Spanish Society of Cardiology

PROMOTER CODE: SEC-DAPATAVI-2020

EudraCT number: 2020-003930-18

COORDINADOR RESEARCHER: Sergio Raposeiras Roubín - University Hospital Alvaro Cunqueiro de Vigo.

PRINCIPAL INVESTIGATOR: _____

CENTER: _____

DOCUMENT VERSION: V1.1. October 2020

Introduction

We inform you about **a research study in which you are invited to participate**. In accordance with current legislation, the study has been approved by the Galician Committee on Drug Research Ethics (CEIm-G), as regulated by Royal Decree 1090/2015 of 4 December, and European Regulation 536/2014 of 16 April. We want you to receive the right and sufficient information so that you can evaluate and judge whether or not you want to participate in this study. To do this, we ask that you read this fact sheet carefully. We will clarify any doubts that may arise. In addition, you can consult with people you trust that you deem appropriate.

VOLUNTEER PARTICIPATION

You should know that your participation in this study is **voluntary** and that you may decide NOT to participate. If you choose to participate, you may change your decision and withdraw consent at any time without justifying such decision. In addition, you should know that in the event of revoking your authorization to participate in this study, this will not alter your relationship with your doctor or cause any harm to your health care.

OBJECTIVE OF THE STUDY

The objective of this study is to investigate whether dapagliflozin treatment is beneficial in patients who have been placed with a percutaneous aortic valve prosthesis due to the presence of severe aortic stenosis.

STUDY DESCRIPTION

The placement of a percutaneous aortic valve prosthesis is an excellent and less aggressive alternative to conventional surgical replacement in patients with aortic stenosis. Despite this, the long-term evolution of these patients is not as favourable as might be expected. Specifically, in patients who have had previous incomes from heart failure, the risk of the patient re-entering for heart failure during the first year is high, which is associated with increased mortality.

Dapagliflozin is a drug that has been shown to reduce mortality and re-entry from heart failure in patients with any of the following conditions: decreased heart contraction force, kidney failure or diabetes mellitus. However, no information is currently available on whether or not dapagliflozin may have clinical benefit in patients undergoing the implantation of an aortic valve prosthesis, especially in terms of reduced heart failure.

In this clinical trial, called "DapaTAVI", we want to study whether receiving dapagliflozin treatment results in a clinical benefit over not receiving it in patients with a history of heart failure who have undergone the implantation of a percutaneous aortic valvular prosthesis.

STUDY ACTIVITIES

At the time of discharge after implantation of a percutaneous aortic valve prosthesis, each patient will be randomly assigned to receive dapagliflozin treatment or not. This means that each patient will have a 50% chance of receiving dapagliflozin or not. A total of **1020 patients (510** treated with dapagliflozin and 510 not treated with dapagliflozin) will be included.

Each patient included in the study will be followed for 1year. Treatment with dapagliflozin (or not dapagliflozin) will be maintained for 1 year, unless your responsible physician decides otherwise, since the opinion of the physician responsible for the study will prevail over any activity of the study.

All patients will be contacted by telephone by the researchers of the study (either researchers from the coordinating center located at the Hospital Alvaro Cunqueiro de Vigo or by the researchers of the hospital where he was recruited for the study) in 2 moments: 3 months and 12 months. In those calls the patient will be asked about their health status, the treatment they continue to take, and whether they have had any hospital admissions. If you have had to be seen in the hospital during that time, your doctor will review the hospital's medical history to document any changes in your clinical situation. In the final telephone contact of the study, after the end of the year of administration of the treatment, the patient will be informed that from that moment he will be treated by his responsible doctor in accordance with the usual clinical practice.

To facilitate centralized monitoring, your name and telephones, in addition to the hospital admission discharge report in which the percutaneous aortic valve prosthesis was implanted, will be shared with the test coordinator team strictly **confidentially** to track within the trial (up to 1 post-TAVI year). Access to the above information is necessary in order to be able to develop this study; however, this access to your personal information will not entail access to the integrity of your medical history by the coordinating team, but only to the information that has been reported to you in previous lines. Only the local investigator dependent on the hospital to which you belong would have access to the integrity of your medical

history.

By participating in this study you will NOT have any additional tests, as this study does not involve any complementary examination or any diagnostic activity ofthe usual clinical practice. All information collected for the study is available for clinical care of your pathological process.

You may contact the researchers in the study at any time for any questions regarding the study (see section "contact in case of doubt").

RISKS AND ANNOYANCES ARISING FROM YOUR PARTICIPATION IN THE STUDY

Dapagliflozin is a **drug authorized by the Spanish Medicines Agency.** Although its current indication is for the treatment of diabetes mellitus, it is currently also being used in non-diabetic patients with heart failure and renal failure, given the benefits observed in 3 large recent clinical trials.

Dapagliflozin is a well-tolerated drug and in most cases, the patient does not experience any side effects. However, due to its mechanism of action, some patient may experience some adverse effect.

The most frequently reported adverse reactions through clinical studies were hypoglycaemia, mainly in patients receiving sulphonylurea treatment, and genital infections. For this reason, patients receiving sulphonylureas are excluded from this study, as well as those patients with recurrent genitourinary infections. Other common adverse reactions include dizziness, rashes, dysuria, polyuria or back pain. It is also important to mention that in data reported in non-diabetic patients with heart failure or renal dysfunction, with more than 4,000 patients, dapagliflozin has not been associated with a higher rate of any significant adverse events compared to placebo, including significant hypoglycaemias.

The dapagliflozin data sheet, which can be consulted on the website of the Spanish Agency for Medicines and Healthcare Products (https://.cima.aemps.es/cima/dochtml/ft/112795007/FT_112795007.html),describes in detail the adverse reactions that have been identified in placebo-controlled clinical studies and post-marketing experience with dapagliflozin. Depending on their frequency, such adverse reactions can be classified into:

- Very common (frequency ≥ 10%): **Hypoglycaemia,** especially when used with sulphonylurea. That is why patients receiving sulphonylureas will not be included in the study (exclusion criterion). In non-diabetic patients, in the DAPA-HF and DAPA-CKD studies, the rates of higher hypoglycaemia with dapagliflozin were less than 1%, with no significant differences from placebo.
- Common (frequency between 1% and 10%): **Genital and urinary tract infections** (vulvovaginal fungal infection, vaginal infection, balanitis, genital fungal infection, vulvovaginal thrush, vulvovaginitis, Candida balanitis, genital thrush, genital infection, male genital infection, penis infection, vulvitis, bacterial vaginitis, vulvar abscess, cystitis, urinary tract infection by Escherichia, infection of the genito-urinary tract, pyelonephritis, trigonitis, Diabetic ketoacidosis, when used in type 1 diabetes mellitus (rates ≤ 0.1% in DAPA-HF and DAPA-CKD studies, with no differences from placebo). Dizziness, Eruption, Back Pain. Dysuria, Polyuria. Increased hematocrit (the mean variation in hematocrit from the initial value was 2.30% with dapagliflozin 10 mg versus -0.33% with placebo. Hematocrit values >55% were reported in 1.3% of subjects treated with dapagliflozin 10 mg versus

0.4% of placebo subjects). **Decreased renal clearance of creatinine** (not observed in the DAPA-CDK study when glomerular filtration was between 25 and 75 ml/min/1.73 m2). **Dyslipidemia** (the average percentage of change from the initial value for dapagliflozin 10 mg versus placebo, respectively, it was: total cholesterol 2.5% versus -0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% vs . -1.0%; triglycerides –2.7% vs . -0.7%).

- Uncommon (frequency between 0.1% and 1%): Fungal infections, volume depletion, thirst, constipation, dry mouth, nicturia, vulvovaginal itching, genital itching, increased blood creatinine during treatment, increased blood urea, weight loss.
- Rare (frequency between 0.01% and 0.1%): Diabetic ketoacidosis in patients with type 2 diabetes mellitus.
- Very rare (frequency < 0.01%): Necrotizing perineum fasciitis (Fournier gangrene), angioedema.

If at any point in the study there were any adverse effects not tolerated or that it posed a risk to the patient's health, or there was any reasonable doubt that this may occur, the trial would be discontinued, and patients would be contacted.

The patient must respond in a responsible manner to the questions asked on the 2 phone visits and must report any adverse events that happen to him or her or changes in medication. You will be warned that, except in case of emergency, do not modify the medication you are taking or take other medicines or "medicinal plants" without first talking to your study doctor.

POSSIBLE BENEFITS

Dapagliflozin may reduce heart failure income after implantation of a percutaneous aortic valve prosthesis or you may not get any health benefits from participating in this study. Regardless of the possible beneficial effect that the drug studied (dapagliflozin) may or may not have, from a personal point of view you are not expected to have a personal benefit from participating in this study.

ALTERNATIVES TO PARTICIPATE:

The alternative to participating in the study is not to participate. **Your health care will never be affected by your decision.** In that case, the prescription of dapagliflozin or will not be at the discretion of your responsible physician, who may choose one or the other option as you deem.

INSURANCE POLICY

The Promoter of the study has an insurance policy that complies with current legislation (Royal Decree 1090/2015) and that will provide you with compensation and compensation in case of impairment of your health or injuries that may occur in relation to your participation in the study, provided that they are not a consequence of the disease itself being studied or the evolution of your disease as a result of the ineffectiveness of the treatment. For more information on this section, consult your primary study researcher at your center.

We inform you that your participation in this clinical trial may change the general and particular conditions (coverage) of your insurance policies (life, health, accident...). Therefore, we recommend that you contact your insurer to determine whether participation in this study will affect your current insurance policy.

PROTECTION OF PERSONAL DATA AND CONFIDENTIALITY

The promoter undertakes to comply with Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights.

The data collected for the study will be pseudonymized, identified by a code, so that it does not include information that can identify you, and only your study doctor/collaborators will be able to relate such data to you and your medical history. Your identity will not be disclosed to any person except exceptions in case of medical emergency or legal requirement. The processing, communication and transfer of personal data of all participants shall comply with the provisions of this law.

Access to your identified personal information will be restricted to the study physician/collaborators, health authorities (Spanish Medicines and Healthcare Products Agency, foreign health authorities), the Research Ethics Committee and staff authorized by the promoter (study monitors, auditors), when they need it to check the data and procedures of the study, but always maintaining the confidentiality of them in accordance with current legislation.

Pseudonymized data will be collected in a **research file responsible** for the institution and will be processed as part of its participation in this study. The Spanish Society of Cardiology (as a promoter) willdouble the relevant measures to ensure the protection of your privacy and will not allow your data to be crossed with other databases that could allow its identification.

Under data protection legislation, you can exercise the **rights of access, modification, opposition and**cancellation ofdata, for which you must contact your study doctor. You also **have the right to limit the processing, restrict or request the deletion of your data.** Of course, you can request a copy of your data or have it forwarded to a third party (right**of portability).** To exercise the rights of access, rectification, deletion and portability of your data, As well as limitation or opposition to its processing, or the right to withdraw consent given or claim with the supervisory authority, you may contact the Principal Investigator of the center (see section "CONTACT IN CASE OF DOUBT") or the Data Protection Officer at the local level (email: _____ Likewise, you have **the right to file a complaint with** the Spanish Data Protection Agency, when you consider that some of your rights have not been respected.

If you decide to withdraw consent to participate in this study, no new data will be added to the database, but those that have already been collected will be used.

The encoded data may be transmitted to third party collaborators of the promoter within the European Union (E.U.) but in no case will contain information that can directly identify you, such as first and last name, initials, address, social security number, etc. In the event of this assignment, it will be for the same purposes of the study described or for use in scientific publications but always maintaining the confidentiality of these in accordance with the legislation in force in the E.U.

At the end of the study the data collected will be deleted after the end of the established legal period (25 years from the end of the trial).

EXPENSES AND ECONOMIC COMPENSATION

Neither the researchers nor the research center receive any compensation within

this investigation. Your participation in the study will not incur any expenses. There will also be no remuneration for you for participating in the study.

OTHER RELEVANT INFORMATION

A description of this clinical trial will be http://reec.aemps.es, as required by Spanish law

Any new information regarding the tests carried out in the study that may affect your willingness to participate in it, and that is discovered during your participation, will be **communicated to you** by your doctor as soon as possible. You should know **that you may be excluded** from the study if the promoter or researchers of the study deem it appropriate, either for safety reasons, for any adverse event or because they consider that you are not complying with established procedures. In either case, you will receive an adequate explanation of the reason for your withdrawal from the study. By signing the accompanying consent sheet, you agree **to** comply with the study procedures set out above.

WHAT TREATMENT WILL I RECEIVE WHEN THE CLINICAL TRIAL ENDS?

When you finish your participation you will receive the best treatment available and your doctor considers the most appropriate for your condition, but you may no longer be given the medication for the study. Therefore, neither the researcher nor the promoter becomes committed to keeping such treatment out of this study.

CONTACT IN CASE OF DOUBTS

If during your participation you have any questions or need more information, please contact Sergio Raposeiras Roubín (principal investigator of the study at the national level) at 986 811 111 ext. 514334 during office hours (from 8 to 15), or in the following email: sergio.raposeiras.roubin@sergas.es at any time.

You can also contact the local study researcher who has invited you to participate in the study, Dr./Dra._____ by email: _____

Thank you very much for your cooperation.

Participant Consent Sheet

ORIGINAL STUDY TITLE: "Dapagliflozin after Transcatheter Aortic Valve Implantation"

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EudraCT number: 2020-003930-18

I, *(name and surname of the participant) .....*
- I have read the fact sheet that has been given to me about the study.
- I've been able to ask questions about the study.
- I've received enough information about the study.
- I have spoken to: *(name of researcher)* ....
- I understand that my participation is voluntary.
- I understand that I can withdraw from the study:
  - Anytime.
  - Without having to explain.
  - Without this impacting my medical care.

☐ I authorize the principal investigator of my center's clinical trial to access those data from my medical history strictly necessary for the development of my participation in it, as well as for the coordinating team to contact me by telephone to track my health status at 3±1 and 12 months.

- **I freely agree to participate in the study.**

Participant Signature: Investigator Signature:

First and last name: First and last name:

Date:____ / __ / ___ Date: ____ / __ /___

Two models must be signed, one will be given to the participant and the other will be retained by the head of the research study

Participant Consent Revocation Sheet

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I, *(name and surname of the participant) .....*

REVOKE my consent to participate in this clinical trial.

Participant Signature:	Investigator Signature:
First and last name:	First and last name:
Date:____ / __ / ___	Date: ____ / __ /___

Two models must be signed, one will be given to the participant and the other will be retained by the head of the research study

Participant's consent to witnesses

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EudraCT number: 2020-003930-18

I, *(first and last name)* ....
as a witness, I say that in my presence
Mr/Mrs.....
has been informed.
You have been read the information sheet that has been given to you about the study.
- He's been able to ask questions about the study.
- You've received enough information about the study.
- You have spoken to: *(researcher's name)* ....
- You understand that your participation is voluntary.
- You understand that you can withdraw from the study:
  - Anytime.
  - Without having to explain.
  - Without this impacting your medical care.

☐ You have authorized the principal investigator of your center's clinical trial to access your medical history data strictly necessary for the development of your participation in your clinic, as well as the coordinating team to contact me by phone to follow up at 3±1 and 12 months.

Signature:	Investigator Signature:
First and last name:	First and last name:
Date:____ / __ / ___	Date: ____ / __ /___

- The study participant has indicated that he/she cannot read/write.
- A study staff member has read the consent document to you, discussed it with the participant, and been given the opportunity to ask questions or consult with others."
- The witness must be an impartial person, outside the studio.

Two models must be signed, one will be given to the participant and the other will be retained by the head of the research study

Revocation of Participant Consent to Witnesses

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I, *(first and last name)* ....
as a witness, I say that in my presence
Mr/Mrs.....
has been informed.
And he/she decided to REVOKE the consent to participate in this Clinical Trial.

Signature:	Investigator Signature:
First and last name:	First and last name:
Date:____ / __ / ___	Date: ____ / __ /___

- The study participant has indicated that he/she cannot read/write.
- A study staff member has read the consent document to you, discussed it with the participant, and been given the opportunity to ask questions or consult with others."
- The witness must be an impartial person, outside the studio.

Two models must be signed, one will be given to the participant and the other will be retained by the head of the research study