Dapagliflozin after Transcatheter Aortic Valve Implantation

- **Identification number**: EudraCT number 2020-003930-18
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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
BNP	B-type natriuretic peptide
CEAC	Clinical Events Adjudication Committee
CFR	Code of Federal Regulations
CI	Confidence Interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CRO	Contract Research Organization
CV	Cardiovascular
DCC	Data Coordinating Center
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HF	Heart Failure
HFrEF	Heart Failure with Reduced Ejection Fraction
HR	Hazard Ratio
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Investigational Review Board
ISO	International Organization for Standardization
ITT	Intention-to-treat
LVEF	Left Ventricular Ejection Fraction

LVH	Left Ventricle Hypertrophy
MI	Myocardial infarction
NIH	National Institutes of Health
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PI	Principal Investigator
PROBE	Prospective, Randomized, Open-label Blinded Endpoint
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVR	Surgical Aortic Valve Replacement
SGLT-2	Sodium-Glucose coTransporter type 2
SMC	Safety Monitoring Committee
TAVI	Transcatheter Aortic Valve Implantation

STATEMENT OF COMPLIANCE

The "Dapagliflozin after Transcatheter Aortic Valve Implantation" (DapaTAVI) trial will be carried out in accordance with Good Clinical Practice (GCP), in accordance with the International Conference on Harmonisation (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46).

The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard to the trial participants.

The Principal Investigator will assure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: Sergio Raposeiras Roubín

PROTOCOL SYNOPSIS

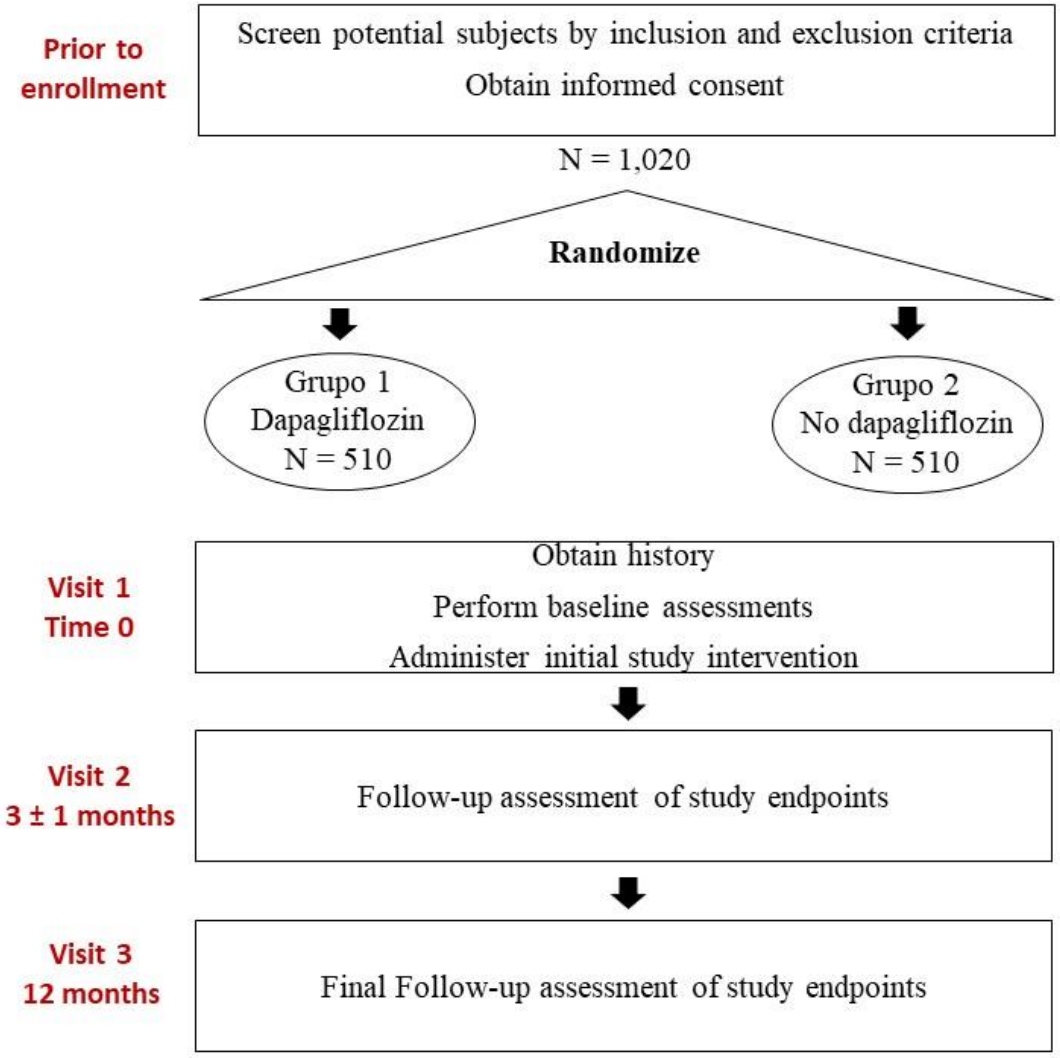
Title	Dapagliflozin after Transcatheter Aortic Valve Implantation (Dapa-TAVI)
Précis	Pragmatic, controlled, prospective, randomized, open-label (open-label), evaluator-blind clinical trial (PROBE design) that will analyze the benefits of dapagliflozin treatment in patients with severe aortic stenosis discharged after implantation of an aortic valve prosthesis transcatheter (TAVI). Patients discharged after TAVI, with a history of heart failure (HF) plus depressed left ventricular ejection fraction (LVEF) (LVEF ≤ 40%) or diabetes mellitus (DM) or glomerular filtration rate (GFR) between 25 and 75 ml/min/1.73 m^2, will be randomized (1:1) before hospital discharge to receive treatment with dapagliflozin 10 mg/day or no dapagliflozin (no placebo). Only variables available during routine clinical practice will be collected and there will be no additional tests. The incidence of clinical events and adherence to the dapagliflozin arm will be documented at 2 timepoints (3 ± 1 months and 12 months) by phone calls and review of medical records.
Level of intervention / pragmatism of the trial	Patients who undergo TAVI for severe aortic stenosis have a non-negligible probability of readmission in the first year for HF, which ranges between 15% and 20%. This rate tends to double in patients with a previous history of HF. Likewise, in patients with moderate-high surgical risk (which are most of patients who undergo TAVI in Spain), post-TAVI mortality in the first year is around 10%. In the last 2 years, dapagliflozin, a Sodium-Glucose Co-Transporter type 2 (SGLT-2) inhibitor, has been shown to significantly reduce cardiovascular mortality and HF admission rate by 17% in 17,160 patients with DM [Study DECLARE-TIMI 38, NEJM 2019], in 26% in 4,744 patients with LVEF ≤ 40% [DAPA-HF Study, NEJM 2019] and in 29% in 4,304 patients with GFR between 25 and 75 ml / min / 1.73 m2 [DAPA-CKD study, presented in August 2020 at the European congress of cardiology, pending publication]. The 3 clinical trials also showed a reduction in total mortality (17% and 31% in DAPA-HF and DAPA-CKD, both significant, and 7% in DECLARE-TIMI-38, not significant), and in none of them an increased rate of adverse events has been seen compared to placebo. Thus, the 3 studies are consistent in reducing CV mortality and readmissions for HF, as well as in terms of drug safety. In post-TAVI patients, there is no standard medical treatment beyond antithrombotic therapy. Based on the 3 previously discussed clinical trials, it is proposed to analyze the possible benefit of prescribing dapagliflozin in post-

	TAVI patients, with a previous history of HF, who have any of these 3 conditions in which dapagliflozin has shown prognostic benefit: ventricular dysfunction (LVEF ≤ 40%), renal dysfunction (GFR 25-75 ml / min / 1.73 m2) or DM. On the basis that dapagliflozin is a licensed drug, the use of dapagliflozin in the present study is supported by 3 published clinical trials with evidence of its efficacy (reduction in mortality and HF) and safety (adverse event rate equal to placebo) , and that the DapaTAVI trial does not require the performance of any additional diagnostic or therapeutic test beyond randomization to dapagliflozin (yes / no), without any additional risk or burden for patients, being a clinical trial independent of the pharmaceutical industry, without no commercial interest, it is considered as a low level of intervention.
Study Duration	3 years. • Recruitment: 2 years • Follow-up: 1 year.
Endpoints	**Primary endpoint:** Incidence rate of the composite of death or worsening heart failure (HF; including hospitalization for HF or an urgent visit resulting in intravenous therapy for HF) **Secondary endpoints:** 1) Incidence rate of individual components of the primary outcome. 2) Incidence rate of cardiovascular (CV) mortality. 3) Incidence rate of atrial fibrillation (AF) **Tertiary endpoints:** 1) Change in functional class (NYHA). 2) Safety endpoints (incidence rate of Major hypoglycemia, Symptomatic hypotension, Genito-urinary infections, Ketoacidosis, Amputation, and Necrotizing Fasciitis of the Perineum (Fournier's Gangrene). 3) Crossovers.
Population	Patients with aortic stenosis and prior history of HF or reduced LVEF discharged after TAVI.
Inclusion criteria	• ≥18 years old. • Severe aortic stenosis underwent TAVI. • Prior heart failure admission and one of the following criteria: ➢ Left ventricular ejection fraction ≤ 40% or ➢ Diabetes mellitus or ➢ Estimated glomerular filtrate rate 25-75 ml/min/1.73 m2
Exclusion criteria	• Known allergy or intolerance to SGLT2 inhibitors. • Concomitant therapy with sulfonylurea or SGLT2 inhibitors. • Systolic blood pressure < 100 mmHg or diastolic blood pressure < 50 mmHg. • An estimated glomerular filtration rate (GFR) below 25 ml per

	minute per 1.73 m2. • Chronic cystitis and/or recurrent urinary tract infections (2 or more in the last year) • Poor control of diabetes mellitus that requires SGLT-2 inhibitor prescription on discharge according to treating physician judge. • Any medical condition that, in the investigator´s judgment, would seriously limit life expectancy (less than one year). • Pregnant or breast-feeding patients • Patients participating in other clinical trials.
Phase	IV.
Number of Sites	26.
Study Drug	Dapagliflozin 10-mg daily dose.
Comparator	Control (no dapagliflozin).
Power calculation	- Anticipated effect size: dapagliflozin treatment will be associated with a 30% reduction in the incidence rate of the primary composite endpoint • Anticipated incidence control arm: 30% • Anticipated incidence in dapagliflozin arm: 21% - Power: 0.8 - Anticipated incidence of withdrawals/losses in follow-up: 5% - Sample size (including withdrawals): 1,020 (510 per treatment arm)
Events adjudication	Events will be adjudicated by a blinded committee after reviewing information sent by local investigators
Interim analyses	Two interim analyses will be performed on primary endpoint and secondary safety endpoints when 33% and 66% of events have been adjudicated (81 and 172 events respectively).
Chronogram	**2021-2024** Q1 2021: Start of inclusion Q1 2022: Half way with inclusion (510 patients) Q1 2023: Anticipated end of inclusion (1,020 patients) Q1 2024: End of follow-up Q2 2024: Reporting primary, secondary, and tertiary outcomes Q3 2024: Subgroups analysis

SCHEMATIC OF STUDY DESIGN

a) Flow Diagram



b) Process Diagram

During hospitalization — **Screening**

- Total n = 1,020
- Obtain informed consent
- Screen potential subjects by inclusion and exclusion criteria
- Obtain history, documents

Pre-discharge — **Randomization**

- Treatment group dapagliflozin: n = 510
- Control group non dapagliflozin: n = 510

Visit 1 At discharge — **Baseline assessments**

- Baseline characteristics and NYHA class
- Laboratory, echocardiographic, and haemodinamic data
- Data about TAVI
- Medical therapy

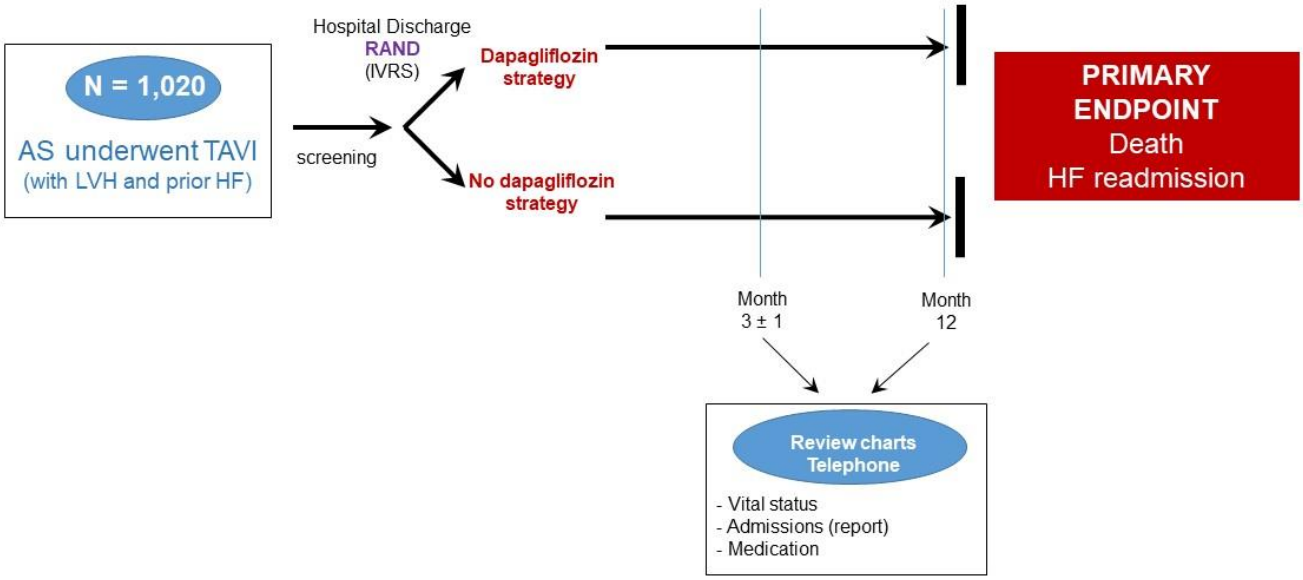
Visit 2 3 ± 1 months — **Follow-up assessments**

- Primary endpoint: death, HF readmission.
- Secondary endpoint: cardiovascular death, AF
- Tertiary endpoints: safety endpoints, NYHA class.
- Change in medication

Visit 3 12 months — **End of Study Assessments**

- Primary endpoint: death, HF readmission.
- Secondary endpoint: cardiovascular death, AF
- Tertiary endpoints: safety endpoints, NYHA class.
- Change in medication
- Optional: echocardiographic data, laboratoy test

c) Timeline Diagram



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- **MONITOR and DATA MANAGER**

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  - Data manager: Sonia Blanco Prieto, Cristina Barreiro Pardal, María Cespón Fernández.

- **CLINICAL EVENTS ADJUDICATION COMMITTEE (CEAC):**

  - Clinical Events Adjudication Committee (CEAC): Rodrigo Estévez Loureiro (director), Iván Núñez Gil, Rocío González Ferreiro, Javier López Pais, María Cespón Fernández.

- **DATA SAFETY MONITORING BOARD (DSMB):**

- It will be assigned later, including at least one expert in biostatistics and 2 experts in cardiology with experience in research / clinical trials.

- **METHODOLOGY LEADERS, STUDY DESIGN & BIOSTATISTICS:**
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  - Sergio Raposeiras Roubín

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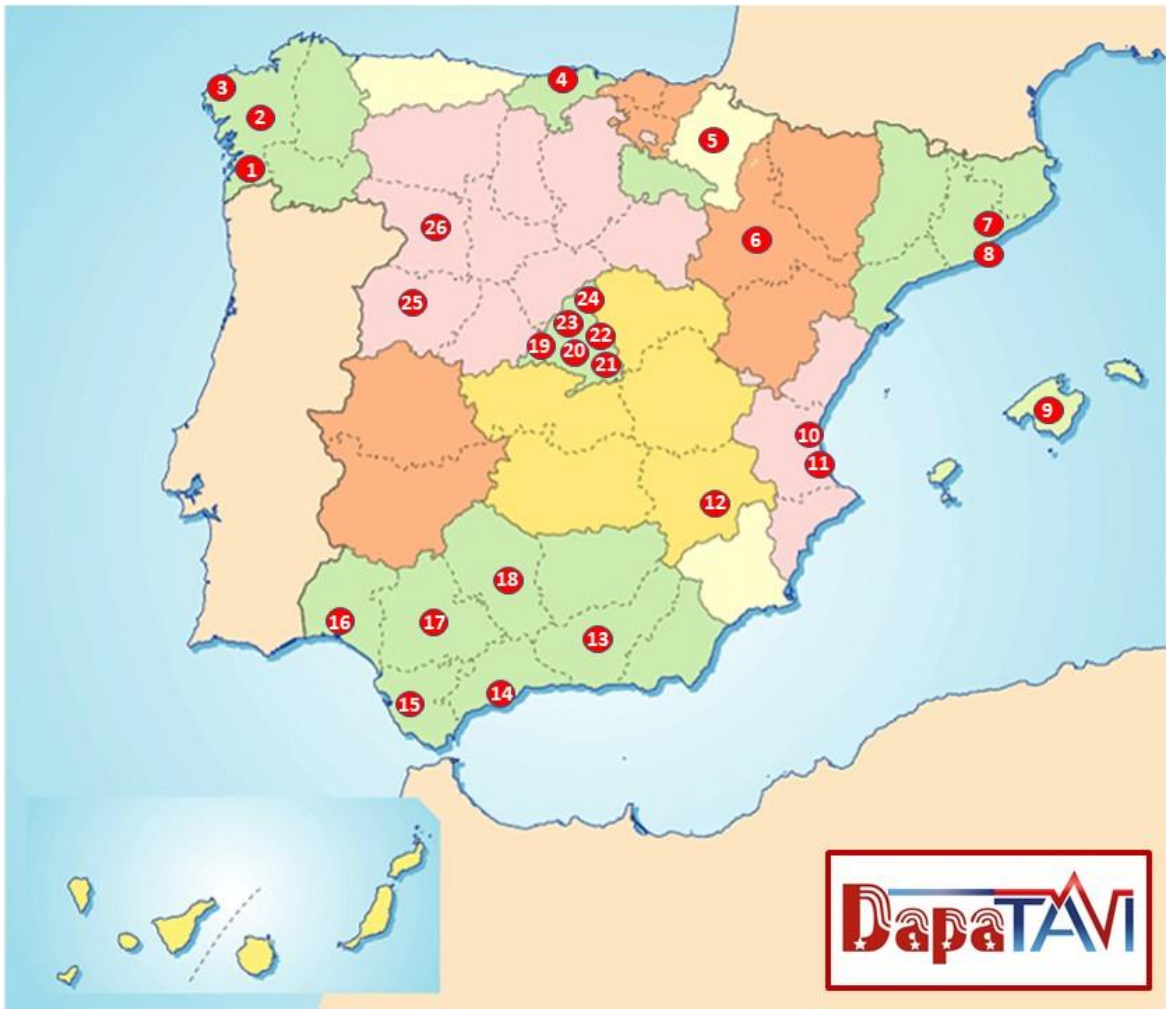


INTRODUCTION

BACKGROUND

Epidemiology and prognosis of aortic stenosis

Aortic valve stenosis (AS) is a progressive disease in which the end stage is characterized by obstruction of left ventricular outf low, resulting in inadequate cardiac output, decreased exercise capacity, heart failure (HF), and death from CV causes. The prevalence of AS is only about 0.2% among adults between the ages of 50 and 59 years but increases to 9.8% in octogenarians, with an overall prevalence of 2.8% in adults older than 75 years of age (1). Although mortality is not increased when aortic stenosis is asymptomatic, the rate of death is more than 50% at 2 years for patients with symptomatic disease unless aortic-valve replacement is performed promptly (2).

The left ventricle in aortic stenosis

AS is associated with left ventricular hypertrophy (LVH), diastolic dysfunction, and decreased longitudinal shortening, although the ejection fraction remains normal in most patients (3). Left atrial enlargement is common owing to elevated left ventricular filling pressures. Pressure overload causes left ventricular remodelling and ultimately LVH. This is often seen as a means of limiting wall stress in order to maintain systolic function (4). Wall stress, by the law of Laplace, is related directly to intracavitary pressure and cavity size, but inversely to wall thickness. The ventricular hypertrophic adaptation follows four well-recognised mechanistic patterns: normal ventricular geometry, concentric remodelling, concentric hypertrophy and eccentric hypertrophy (5). Concentric remodelling is defined by a normal left ventricular mass and an increased relative wall thickness and concentric hypertrophy by a combination of LVH and increased relative wall thickness. There is evidence to suggest that adaptive remodelling becomes maladaptive with increasing LVH and consequent myocardial fibrosis. A study by Cioffi et al. showed that over 10 % of patients with asymptomatic severe AS exhibited inappropriate LVH and these patients had a 4.5-fold higher risk of death or hospital admission (6). LVH is associated with myofibrillar hypertrophy, but also fibrosis, which is the deposition of collagen and fibronectin.

Echocardiographic studies, however, have also demonstrated that 10–20 % of patients with AS do not have LVH (6).

Interventions in aortic stenosis: TAVI

AS is a slowly progressive disease but is associated with dismal outcomes within a few years after symptom emergence if not treated with aortic valve replacement (AVR) (7). Surgical aortic valve replacement (SAVR) had been the only effective treatment for severe AS for many years. However, transcatheter aortic valve implantation (TAVI) has emerged as an effective alternative to SAVR, demonstrating short-term and mid-term outcomes comparable or even superior to SAVR regardless of the surgical risk of the patients (8).

Clinical outcomes after TAVI

TAVI has transformed the treatment of severe AS. However, questions remain regarding the long-term outcomes of this procedure.

- **Mortality:** Although TAVI is associated with a significant reduction in mortality compared to conservative management, the incidence of death is not negligible at one year. In the 3 cohorts of PARTNER (Placement of AoRTic traNscathetER valve) trial, 1-year mortality was 1.1%, 11.8% and 30.7% in low, moderate, and high risk patients (9-11), respectively. In real world patients, the 1-year mortality ranges from 10 to 20% (11, 12), depending on the patient's risk.
- **Heart Failure (HF):** HF is responsible of 15% of mortality in TAVI patients. The group of Alain Cribier reported a rate of 1-year HF admission of 24.1% after TAVI (13) , being significantly lower in other studies (± 15%) (12, 14). The HF admission rate is twice in patients with prior HF admissions before TAVI (13), and it is also increased in patients with high levels of NTproBNP (14) .

SCIENTIFIC RATIONALE

Impact of Dapagliflozin in reduction of HF readmissions

Accumulating mechanistic insights suggest that sodium–glucose co-transporter 2 (SGLT-2) inhibitors ─especially dapagliflozin and empagliflozin─ may be valuable in the treatment of HF regardless of diabetes mellitus (DM) status and LVEF. SGLT-2 inhibitors may exert cardioprotective effects through several distinct mechanisms, including:

- Improvement in ventricular loading conditions secondary to reductions in preload ─mediated by osmotic diuresis and natriuresis─ (15) and afterload (potentially occurring via lowering of arterial pressure and stiffness) (16).
- Provision of an alternative cardiac energy supply in the form of cardiac ketones ─specifically β-hydroxybutyrate─ (17).
- Direct inhibition of the sodium/hydrogen (Na+/H) exchanger in the myocardium, leading to reduction in or reversing of cardiac injury, hypertrophy, fibrosis, remodeling, and systolic dysfunction (18).
- Reduction in left ventricular mass and improvement in diastolic function through inhibition of cardiac fibrosis ─a feature of HF─ (19).
- Improvement in endothelial dysfunction (20).
- Stimulation of increased glucagon secretion, potentially improving cardiac performance by either increasing cardiac index and fuel availability or decreasing peripheral vascular resistance (21).

Patients with HF, regardless of LVEF, have sodium and fluid retention as well as coronary, myocardial, and systemic endothelial dysfunction, even in the absence of overt DM (22). As the natriuretic ─most notably─, glucosuric, and metabolic effects of SGLT-2 inhibitors have been demonstrated in patients with and without DM, it has been postulated that SGLT-2 inhibitors may benefit patients with HF regardless of DM status (23). This has been demonstrated in several preclinical studies (24, 25). In a preclinical model of HF, empagliflozin treatment (or gene knockout simulation of SGLT-2 inhibition) improved cardiac function (17). In preclinical models of myocardial

infarction, dapagliflozin has demonstrated attenuation of cardiac fibrosis, and empagliflozin has been shown to improve cardiac function and remodeling (24). In other experimental models of HF without diabetes mellitus, empagliflozin prevented worsening of cardiac function (17).

Two clinical trials with SGLT-2 inhibitors have shown benefit in patients with HF with HF and reduced ejection fraction (HFrEF) ─regardless of DM status─. The DAPA-HF trail, with dapagliflozin, was presented in European Society of Cardiology (ESC) Congress 2019, with 30% reduction of HF readmission and 17% reduction of all-cause death (26). The EMPEROR reduced HF will be presented soon, but it has already been advanced that empagliflozin reduced the primary end-point of death and HF. After a fast-track designation and priority review, the US FDA approved dapagliflozin on 5/5/2020 to reduce the risk of cardiovascular death or hospitalization in patients with HFrEF with or without Type 2 diabetes.

Recently, the results of DAPA-CKD trial were presented in ESC Congress 2020 (Paris, September 2020), showing a benefit of dapagliflozin in reducing mortality and worsening HF in patients with an estimated glomerular filtrate rate (eGFR) 25-75 ml/min/1.73 m2.

Possible benefit of Dapagliflozin in TAVI patients

Almost 1 out of 3 of the patients with severe aortic stenosis and prior admissions by HF who underwent TAVI are readmitted in the first year after TAVI due to HF (13, 14). Furthermore, 1 out of 10 patients dies in the first year after TAVI (12). A recent study showed that the regression of left ventricular mass after TAVI was associated with with lower death and hospitalization rates (27).

Dapagliflozin demonstrated a nearly 30% reduction in readmissions for HF in the DECLARE and DAPA-HF clinical trials (26, 28), for patients with reduced LVEF or DM and high CV risk. Recently, another clinical trial (DAPA-LVH) showed that dapagliflozin treatment significantly reduced left ventricular mass in patients with LVH (29). The regression of left ventricular mass suggests dapagliflozin can initiate reverse

remodelling and changes in left ventricular structure that may partly contribute to the cardio-protective effects of dapagliflozin.

The DapaTAVI trial is a controlled randomized clinical trial that will address whether dapagliflozin therapy after TAVI reduces the incidence of major clinical events (mortality and HF readmission) in patients with aortic stenosis and history of prior HF, and one of the following conditions: DM, or LVEF ≤ 40%, or eGFR 25-75 ml/min/1.73 m2. The justification for undertaking a trial like DapaTAVI is based on the comments above. We propose a clinical trial with dapagliflozin ─drug that reduces HF and CV death, in addition to causing ventricular mass regression─ in TAVI patients ─population at high risk of death and HF readmission─.

Currently there is no study about medical therapy with SGLT-2 inhibitors in patients with TAVI. DapaTAVI trial will fill this gap and will contribute refining the treatment of TAVI patients across the world.

OBJECTIVES AND PURPOSE

The objective of the DapaTAVI trial is to investigate the effects dapagliflozin therapy on mortality and CV morbidity in patients with severe aortic stenosis and previous admission for HF undergoing TAVI with any of these 3 medical conditions: DM, LVEF ≤ 40% or renal dysfunction (GFR 25-75 ml / min / 1.73 m2)

HYPOTHESES

Main hypotheses:

1) Dapagliflozin therapy in TAVI patients with prior history of HF and diabetes mellitus, reduced LVEF (LVEF ≤ 40%) or renal dysfunction (eGFR 25-75 ml/min/1.73 m2), is associated with reduced 1-year mortality or worsening of HF.

Secondary hypotheses:

1) Dapagliflozin therapy in TAVI patients with prior history of HF and diabetes mellitus, reduced LVEF (LVEF ≤ 40%) or renal dysfunction (eGFR 25-75 ml/min/1.73 m2), is associated with reduced 1-year CV mortality
2) Dapagliflozin therapy in TAVI patients with prior history of HF and diabetes mellitus, reduced LVEF (LVEF ≤ 40%) or renal dysfunction (eGFR 25-75 ml/min/1.73 m2), is associated with reduced 1-year incidence of AF.
3) Dapagliflozin therapy in TAVI patients with prior history of HF and diabetes mellitus, reduced LVEF (LVEF ≤ 40%) or renal dysfunction (eGFR 25-75 ml/min/1.73 m2), is associated with improvement in functional class.

STUDY DESIGN AND ENDPOINTS

DESCRIPTION OF THE STUDY DESIGN

Dapa-TAVI is a pragmatic, controlled, prospective, randomized, open-label blinded endpoint (PROBE design) clinical trial. Patients being discharged after TAVI who meet all inclusion criteria, and none of the exclusion criteria, will be eligible for the enrollment. Patients will be 1:1 randomized to 1 of these 2 arms:

- **Intervention group:** Sodium-glucose cotransporter-2 (SGLT-2) inhibitor therapy with daily oral dose of dapagliflozin 10 mg.
- **Control group:** no SGLT-2 inhibitor therapy with dapagliflozin.

Apart from dapagliflozin therapy (or control), patients will be treated according to current standards (per managing physician prescription).

STUDY ENDPOINTS

➢ PRIMARY ENDPOINT

- Incidence rate of the composite of all-cause mortality or worsening HF (including hospitalization for HF or an urgent visit resulting in intravenous therapy for HF).

➢ SECONDARY ENDPOINTS

- Indicence rate of individual components of primary endpoint.
- Incidence rate of CV death.
- Incidence rate of atrial fibrillation (AF).

➢ TERTIARY ENDPOINTS

- Improvement in NYHA class.
- Safety endpoints:
  - Symptomatic hypotension. Symptomatic hypotension includes postural dizziness with systolic blood pressure < 100 mmHg, and orthostatic hypotension (defined as a decrease of >20 mmHg in systolic blood

pressure or >10 mmHg in diastolic blood pressure from a supine to a standing position).

- Major hypoglycemia. Major hypoglucemia is defined as an event where all the following criteria were confirmed by the investigator: (1) the patient experienced symptoms of severe impairment in consciousness or behaviour; (2) the patient needed external assistance; (3) intervention was needed to treat the hypoglycaemia; and (4) there was prompt recovery of acute symptoms following the intervention.
- Ketoacidosis.
- Genital or Urinary Infections
- Amputation
- Necrotizing Fasciitis of the Perineum (Fournier's Gangrene)

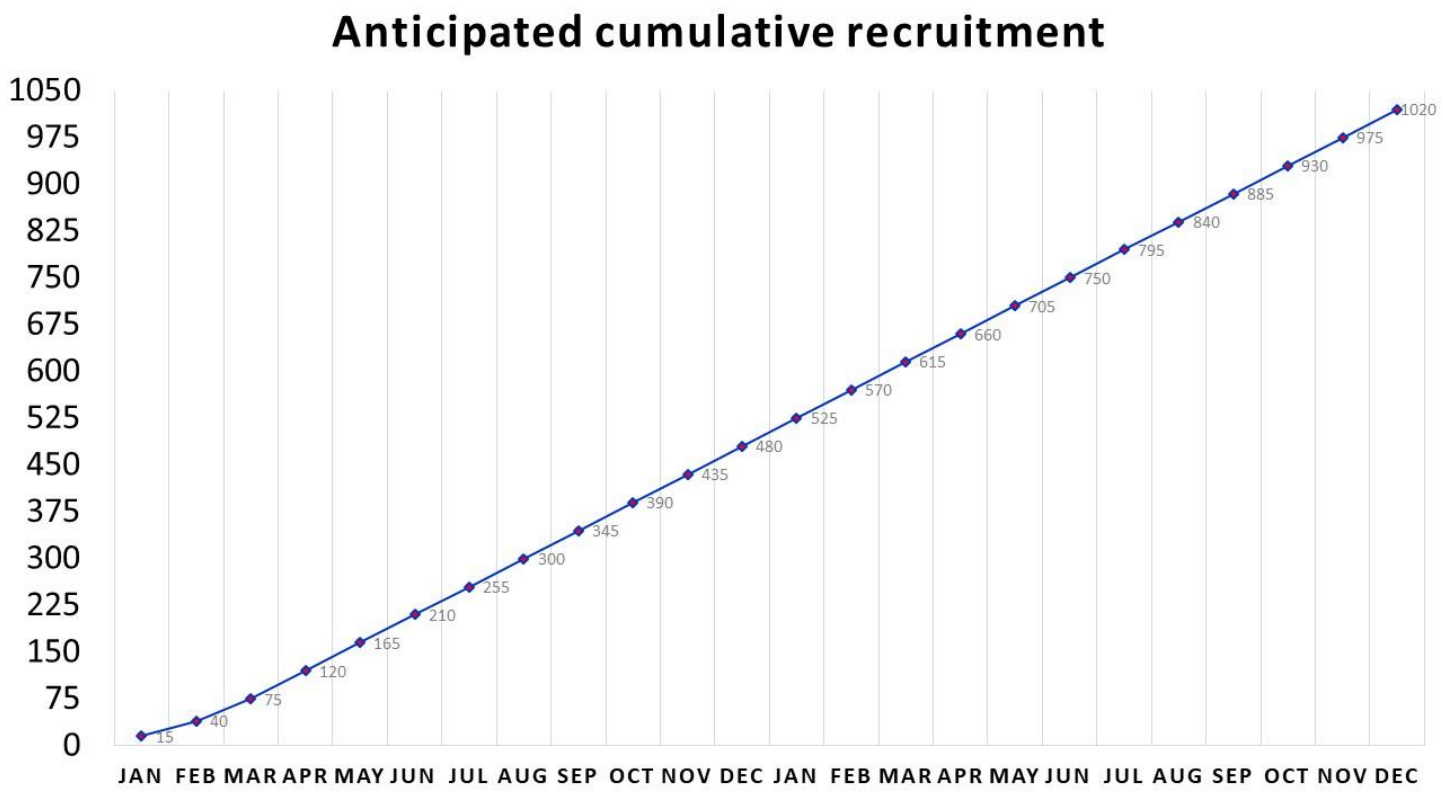
▪ Crossovers (incidence rate and reasons).

STUDY ENROLLMENT AND WITHDRAWAL

Estimated date to initiate enrollment is Q1 2021. It is anticipated that enrollment will be performed in a 2 years time frame. Screening of patient candidates will be done during index hospital admission (i.e. admission for TAVI). Individuals meeting inclusion criteria (and not meeting any exclusion criterion) will be invited to participate immediately before hospital discharge. Patients may be recruited after hospital discharge as long as randomization is one within two following weeks after TAVI.

Women and members of minority groups and their subpopulations will be included in accordance with the NIH (National Institutes of Health) Policy on Inclusion of Women and Minorities as Participants In Research Involving Human Subjects.

Anticipated recruitment rate.



PARTICIPANT INCLUSION CRITERIA

- Patients (≥18 years, both genders) with severe aortic stenosis (aortic valve area ≤ 1.0 cm2, or indexed aortic valve area ≤ 0.6 cm2/m2, or jet velocity ≥ 4.0 m/s, or mean gradient ≥ 40 mmHg) underwent TAVI.
- Prior heart failure admission and one of the following criteria:
  - Left ventricular ejection fraction ≤ 40% or
  - Diabetes mellitus or
  - Estimated glomerular filtrate rate 25-75 ml/min/1.73 m2

PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1) Known allergy or intolerance to SGLT2 inhibitors.
2) Concomitant therapy with sulfonylurea or SGLT2 inhibitors.
3) Systolic blood pressure < 100 mmHg or diastolic blood pressure < 50 mmHg.
4) An estimated glomerular filtration rate (GFR) below 25 ml per minute per 1.73 m2.
5) Chronic cystitis and/or recurrent urinary tract infections (2 or more in the last year)
6) Poor control of diabetes mellitus that requires SGLT-2 inhibitor prescription on discharge according to treating physician judge.
7) Any medical condition that, in the investigator´s judgment, would seriously limit life expectancy (less than one year).
8) Pregnant or breast-feeding patients
9) Patients participating in other clinical trials.

DEFINITIONS AND EVENT ADJUDICATION

DEFINITION FOR EVALUATIONS OF EVENTS DURING FOLLOW-UP

- **Worsening HF:** including hospitalization for HF or an urgent visit resulting in intravenous therapy for HF, similar as was previously defined in DAPA-HF trial.
- **HF admission:** the definition of HF admission is adapted from the 2016 European Society Guidelines (ESC) Guidelines (30) and from the document published by the American College of Cardiology (ACC) and American Heart Association (AHA) working group to standardize clinical data (31). A HF Hospitalization is defined as an event that meets ALL of the following criteria:

  1) The patient is admitted to the hospital with a primary diagnosis of HF.

  2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable).

  3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least ONE of the following:
     a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea).
     b. Decreased exercise tolerance.
     c. Fatigue.
     d. Other symptoms of worsened end-organ perfusion or volume overload (as determined by the medical judgement of the investigator).

  4) The patient has objective evidence of new or worsening HF, consisting of at least TWO physical examination findings OR one physical examination finding and at least ONE laboratory criterion, including:

a. Physical examination findings considered to be due to heart failure, including new or worsened:
    - Peripheral edema.
    - Increasing abdominal distention or ascites (in the absence of primary hepatic disease).
    - Pulmonary rales/crackles/crepitations.
    - Increased jugular venous pressure and/or hepatojugular reflux.
    - S3 gallop.
    - Clinically significant or rapid weight gain thought to be related to fluid retention.

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
    - Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
    - Radiological evidence of pulmonary congestion.
    - Non-invasive diagnostic evidence of clinically significant elevated left- or rightsided ventricular filling pressure or low cardiac output. For example echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract minute stroke distance (time velocity integral).
    - Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m2

5) The patient receives initiation or intensification of treatment specifically for HF, including at least ONE of the following:
    a. Augmentation in oral diuretic therapy.
    b. Intravenous diuretic or vasoactive agent (e.g., inotrope, vasopressor, or vasodilator).
    c. Mechanical or surgical intervention, including:
        - Mechanical circulatory support (e.g. intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart).
        - Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

- **Urgent visit for HF:** any unplanned visits for HF decompensation resulting in intravenous therapy for HF, including diuretic or inotropic drugs.
- **Death:** All deaths reported post-randomization, except for patients who have withdrawn their consent, should be adjudicated. Deaths will be sub-classified by CV, non-CV primary cause or undetermined cause of death. Classification of deaths as CV or non-CV is aimed at capturing the primary cause of death. The primary cause as defined here is the underlying disease or injury that initiated the train of events resulting in death.
- **Cardiovascular (CV) death**: CV deaths include deaths that result from an myocardial infarction, sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes (31).

1. Death due to Acute Myocardial Infarction (MI): refers to a death within 30 days after a myocardial infarction (MI) related to consequences seen immediately after the myocardial infarction, such as progressive congestive HF, inadequate cardiac output, or refractory arrhythmia. If these events occur after a “break” (e.g., a HF and arrhythmia free period), they should be designated by the immediate cause. The acute MI should be verified by the diagnostic criteria outlined for acute MI (including autopsy findings showing recent MI or recent coronary thrombus) and there should be no conclusive

evidence of another cause of death. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new left left bundle branch block and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood should be considered death due to acute MI. Death resulting from a procedure to treat myocardial ischemia or to treat a complication resulting from myocardial infarction should also be considered death due to acute MI. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and electrocardiographic (ECG) evidence. Death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

2. Sudden Cardiac Death: refers to death that occurs unexpectedly and includes the following deaths:
    a. Death witnessed and instantaneous without new or worsening symptoms.
    b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms.
    c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording or witnessed on a monitor by either a medic or paramedic, or unwitnessed but found on implantable cardioverter-defibrillator review).
    d. Death after unsuccessful resuscitation from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology.
    e. Death > 24hrs after a patient has been successfully resuscitated from cardiac arrest and without identification of a non-CV etiology.
    f. Unwitnessed death in a subject seen alive and clinically stable ≤ 24 hours prior to being found dead without any evidence supporting a

specific non-cardiovascular cause of death (information regarding the patient's clinical status preceding death should be provided, if available.

3. Death due to HF or Cardiogenic Shock: refers to death occurring in the context of clinically worsening symptoms and/or signs of HF not in the context of an acute MI and without evidence of another cause of death. New or worsening signs and/or symptoms of congestive HF include any of the following:
    a. New or increasing symptoms and/or signs of HF requiring the initiation of, or an increase in, treatment directed at HF or occurring in a patient already receiving maximal therapy for HF.
    b. Heart failure symptoms or signs requiring continuous intravenous drug therapy or oxygen administration.
    c. Confinement to bed predominantly due to heart failure symptoms.
    d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF.
    e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening HF. Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion: Cool, clammy skin; or oliguria (urine output < 30 mL/hour); or cardiac index < 2.2 L/min/m2. Cardiogenic shock can also be defined as systolic blood pressure ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour. This category will include sudden death occurring during an admission for worsening HF.

4. Death due to Stroke: refers to cerebrovascular event the sequelae of which lead to death, generally within 30 days. The cerebrovascular event should be verified by the diagnostic criteria outlined for cerebrovascular events (including autopsy findings) and there should be no conclusive evidence of another cause of death.
5. Death due to CV Procedures: refers to death caused by the immediate complications of a cardiac procedure.
6. Death due to CV Haemorrhage: refers to death related to haemorrhage such as a non-stroke intracranial haemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or haemorrhage causing cardiac tamponade.
7. Death due to Other CV Causes: refers to a CV death not included in the above categories but with a specific, known cause (e.g., pulmonary embolism or peripheral arteria disease).

- **Non-CV Death:** Non-CV death is defined as any death not covered by CV death and falling into one of the following categories:
  1. Pulmonary failure
  2. Renal
  3. Gastrointestinal causes
  4. Hepatobiliary
  5. Pancreatic
  6. Infection (includes sepsis)
  7. Inflammatory (e.g., Systemic Inflammatory Response Syndrome / Immune (including autoimmune, may include anaphylaxis from environmental (e.g., food allergies)
  8. Haemorrhage that is neither CV bleeding or stroke
  9. Non-CV procedure or surgery
  10. Trauma
  11. Suicide
  12. Non-prescription drug reaction or overdose

13. Prescription drug reaction or overdose
14. Neurological (non-cardiovascular)
15. Malignancy
16. Other, please specify.

- **Undetermined Cause of Death:** Undetermined Cause of Death refers to a death not attributable to one of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few patients in well-run clinical trials.
- **Atrial fibrillation (AF):** The diagnosis of AF is based on the physical finding of an irregular supraventricular heart rhythm and is confirmed with an ECG or rhythm strip.
- **Functional status**: Functional status will be measured as New York Heart Association (NYHA) functional classification of heart failure for dyspnea.

EVENT ADJUDICATION

Once a potential event is detected either by a local investigator or during a follow-up, a report from the hospital in which the patient is admitted will be requested (with any personal identification of the patient blinded). All events need to be adjudicated by the Clinical Events Adjudication Committee (CEAC). For the evaluation of the events, the local investigator should prepare anonymous copies of the original source of data (clinical reports, complementary tests [catheterizations, ECG, X-ray, etc], lab tests and all relevant information). The regional PI will be responsible for sending the information confidential to the scientific project manager, who will prepare documentation for the CEAC. The CEAC will have a chairman and 3 additional

members. All events will be evaluated by at least 2 members of the CEAC. In the case of controversies, the opinion of the chairman will prevail.

Patients will be followed up for the entire duration of the study regardless of having an adjudicated event. For the composite primary endpoint, the first event will be included in analysis, but for secondary endpoints, different events in the same patients will be individually evaluated.

CENTERS SELECTION

Any center with TAVI program is eligible to participate. During hospital selection, the number of patients discharged with a TAVI during the past 12 months will be evaluated. A minimum number of patients per year (n=12) will be agreed with the hospital. Hospitals not fulfilling the agreed number will eventually be disqualified from recruitment. Hospital with electronic medical records will be prioritized.

RANDOMIZATION AND STRATEGIES FOR RECRUITMENT

Patients will be screened during index hospitalization for TAVI. At discharge (or after discharge provided randomization takes place within 14 days after TAVI), and after informed consent is signed, patients will be randomized to receive or not dapagliflozin. After discharge, patients will be included in each center's TAVI follow-up program (as per local practice).

Randomization will be done via web or via a dedicated mobile application. Each investigator participating in the trial will have a log-in username and password that links her/him to a specific hospital. During randomization, ten fields will be needed to complete:

1. Full name of patient
2. Telephones (personal and that from relatives)
3. Date of TAVI
4. DM status.
5. Age
6. Sex
7. Creatinine (mg/dL)
8. LVEF (%).
9. Does the patient meet all the inclusion criteria and none of the exclusion criteria? (Yes / No, they can only be randomized if yes is selected).
10. Has the patient signed informed consent? (Yes / No, they can only be randomized if yes is selected)

Data will be stored in a secure server located at the Coordinator Center (Hospital Álvaro Cunqueiro, Vigo) and will be kept confidential according to legal regulations for data protection.

FOLLOW-UP STRATEGIES

Follow-up will consist on telephone calls and review of patients' medical records.

Once a local investigator identifies that a patient has been admitted for something potentially relevant to the study, he/she will be responsible for collecting the information (admission report, tests, etc..) and send it blinded to the central site for blinded event adjudication.

Follow ups will be done at 2 timepoints: 3±1, 12 months.

PATIENT ENGAGEMENT / RETENTION STRATEGIES

After randomization, each patient will receive a card identifying the clinical trial that will contain a brief explanation of the aims of it. In the trial card, the arm in which the patient was included (dapagliflozin yes or no) will be stated, together with a central telephone number and email. The patient will be encouraged to contact (phone call/email) for any question related to the trial (either from the patients or from any physician seeing the patient). Any change related to dapagliflozin therapy (stop or initiate dapagliflozin) will be ideally communicated before implementation so the research team can annotate the reasons for the change. Moreover, any change in clinical status (admissions, symptoms, etc..) related to the study may be reported using this telephone number or email. Patients will be asked to carry the study card always with them to facilitate interaction.

No incentives will be established for participating in the study.

PARTICIPANT WITHDRAWAL

Given that this is an open label study with an approved medication and crossovers are not a criterium for withdrawal from the study (see below), the only reason for patient withdrawal from the study is the willingness of the patient to be excluded from the trial.

CROSSOVERS

Crossovers (stop dapagliflozin therapy in the dapagliflozin treatment arm or initiate dapagliflozin in the control arm) will be indicated clinically by treating physicians. Patients and any treating physician will be asked to call the central coordinating center to discuss any crossover before taking the decision. Any decision will always be made by treating physician, but these will be encouraged to do so only if there is a clear clinical indication for it.

Crossovers will be annotated along with the main reason driving the change. Patients with crossover will remain in the trial and follow ups will be done as per protocol. Since the main endpoint of the study is in an intention-to-treat basis, patients will be analyzed according to randomization regardless crossovers. Post-hoc analysis will take into consideration crossovers and patients adhering to original randomization arm during the entire follow-up of the study will be analyzed (see pre-specified groups).

PREMATURE TERMINATION OF STUDY

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the IP to the IRB.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.

DAPAGLIFLOZIN THERAPY STRATEGY

TREATMENT DURING TAVI HOSPITALIZATION (i.e. before randomization)

During the inhospital phase, patients will be treated based on the clinical judgment of their responsible physician, strongly suggesting adherence to the recommendations of Clinical Practice Guidelines.

SGLT-2 THERAPY BEFORE RANDOMIZATION

Randomization for DapaTAVI is at the time of discharge or after hospital discharge (in this case always within 14 first days after TAVI), thus treatment during index hospitalization (i.e. before randomization) is completely at the discretion of the treating physician. Patients receiving SGLT-2 inhibitors before randomization will not included in the trial.

DAPAGLIFLOZIN THERAPY AFTER DISCHARGE (i.e. after randomization)

- **DAPAGLIFLOZIN DOSING:** Dapagliflozin 10 mg once a day.
- **ROUTE OF ADMINISTRATION:** oral.
- **ACQUISITION OF STUDY MEDICATION:** This is a pragmatic trial and dapagliflozin therapy is included in the clinical practice armamemtarium. Thus, prescription of dapagliflozin agent will be done by physicians according to randomization arm. The study will not provide with any medication to the study.
- **DURATION OF THERAPY:** The patient will be maintained with / without dapagliflozin throughout the study period (1 year) if no crossover occurs (see specific section).

MANAGEMENT OF PATIENTS AFTER A THE OCCURRENCE OF AN EVENT

When a patient suffers a clinical event (included or not in the list of clinical endpoints), treating physicians are encouraged to contact the coordinating center and local PI. Patients suffering a clinical endpoint (including those included in the primary composite) will remain in the study and should undergo the scheduled follow-ups.

In the case that a patient suffers any clinical endpoint, it is strongly recommended to manage the patients according to Clincal Practice Guidelines. If the physician feels appropriate to initiate or to stop SGLT-2 inhibitor therapy, this will always prevail. Crossover will be annotated and patients followed-up according to original plan.

In all cases, cardiologists from the research team will be available anytime for discussion about the management of patients.

DATA COLLECTION and STUDY PROCEDURES

STUDY EVALUATIONS / TESTS

DapaTAVI is a pragmatic open label randomized clinical trial. There are no medical specific procedures apart from telephone follow ups and registries consultation. No medical exams or tests will be performed for the study matter. All exams and actions are those clinically indicated and the study investigators will collect data from clinical records.

DATA RECORDING

The following variables will be collected and included in the web-based eCRD.

BASELINE VARIABLES TO COLLECT

Number	Variable
Demographic and antropometric data	
1	Age
2	Sex
3	Weight
4	Height
Cardiovascular risk factors	
5	Hypertension
6	Diabetes mellitus
Cardiovascular history	
8	Peripheral artery disease
9	Ischemic heart disease
10	Prior myocardial infarction
11	Prior stroke
12	Atrial fibrillation
13	Bundle branch block prior to TAVI
14	Prior pacemaker
15	Prior aortic bioprothesis
16	Prior valvuloplasthy
Comorbidity	
17	Chronic obstructive pulmonary disease
18	Chronic kidney disease
Echocardiographic data (prior to TAVI)	
19	Left ventricular ejection fraction

20	Aortic valve area
21	Mean gradient
22	Left ventricular hypertrophy
23	Moderate-severe mitral regurgitation
Laboratory data (prior to randomization)	
24	Hemoglobin
25	Creatinine
26	NTproBNP
Complications post TAVI (prior to randomization)	
27	Bundle branch block
28	Moderate-severe aortic regurgitation
29	Left ventricular ejection fraction
30	Need of pacemaker
Medical therapy at discharge	

WEBSITE AND MOBILE APP: RANDOMIZATION AND ELECTRONIC CASE REPORT FORM (eCRF)

DapaTAVI Website

There will be a wesite with a general information of the trial available to the general public (pre-loggin). Each investigator will have a username and password allowing her/him to enter the post-loggin site. The username/password identifies the center of the investigator (information used for randomization).

After loggin there will be several options, including download protocol, download inform consent forms, download participant identification cards, and check mach of the trial.

DapaTAVI MOBILE APP

There will be a mobile phone application containing most of the information in the website. The main purpose of the mobile app is to facilitate recruitment.

RANDOMIZATION SYSTEM

Once a patient is ready to be included in the trial, and after informed consent has been signed, researchers will click the "Randomize a new patient" button. Eight fields will be requested (see specific section above) and then the patient Study Number and treatment allocation will be displayed.

1. Full name of patient
2. Telephones (personal and that from relatives)
3. Date of TAVI
4. DM status.
5. Age
6. Sex
7. Creatinine (mg/dL)
8. LVEF (%).
9. Does the patient meet all the inclusion criteria and none of the exclusion criteria? (Yes / No, they can only be randomized if yes is selected).
10. Has the patient signed informed consent? (Yes / No, they can only be randomized if yes is selected)

When accesing via mobile app, randomization will be done after entering the eight fields.

eCRF SYSTEM

To complete baseline and follow-up data, another button will bring researcher to the electronic case report form (eCRF). There will be a web-based eCRF to upload the information required for this trial (see section Data collection).

CENTRAL eCRF COMPLETENESS: UPLOAD DISCHARGE REPORTS

Researchers will be offered with the possibility of completing baseline variables by the coordinating center (University Hospital Álvaro Cunqueiro, Vigo, Spain). For this purpose, a copy of the admission report will be requested. To comply with the protection data law, the admission reports should be sent in a secure system.

When accesing via website, there will an option for "upload admission report". The file containing the report (.pdf or .doc) will be selected and uploaded in the system. Since the variables collected in DapaTAVI are those clinically available, it is expected that most of the information will be contained in the admission report.

When accesing via mobile app, there will a possibility of taking a photograph of the admission report with the mobile camera. To avoid retention of photos of the admission report in the mobile phones, the app will not allow selection of previously done photos, only a direct access to the camera via app.

FOLLOW-UP PROCEDURES

- **Specific study follow-up**. All patients will be monitored by telephone and through their medical records at 3±1 and 12 months, to know their vital status, development of an end-point event or any adverse effect. Whenever a patient presents a clinical event, the medical history will be requested to the local PI. For the DapaTAVI trial, no specific ECG, echocardiogram, or laboratory monitoring are need, only clinical data.

  Local researchers will be offered with the possibility of doing telephone calls from the national coordinating center (Hospital Álvaro Cunqueiro, Vigo, Spain). This will be agreed at the beginning of the study or anytime during the march of the trial (i.e. if a center initially is willing to do telephone follow-ups but later thinks this is not possible, the coordinating center will take over this responsibility anytime).

  On phone calls, the following fields will be completed after interacting with the patient/family:

  1. Vital status (alive/death). If death, cause of death (cardiovascular, non-cardiovascular).
  2. Any HF hospital readmissions or visit to the emergency department (yes/no).

     When the patient died or was admitted to a hospital for any cause which may be related to any of the study endpoints, medical reports will be requested to the local investigator.
  3. Adherence to randomization arm (yes/no). If no, date (month/year) of crossover, and reason for crossover (free text field).
  4. Functional health status by the NYHA scale.

- **General monitoring.** All patients will receive the usual follow-up performed at their center for patients after TAVI. Once a potential event is detected either by a

local investigator, a report from the local investigator should be sent to the coordinating center for the evaluation by the adjucation committee.

Specific data: Al investigators will be encouraged to report information about ECG, analytical, and echocardiographic data throughout the first year.

DATA SAFETY MONITORING BOARD (DSMB)

A Data Safety Monitoring Board (DSMB) will be established to formally review the accumulating data from this trial to ensure there is no avoidable increased risk for harm to subjects. Two interim analyses will be performed on primary endpoint and secondary safety endpoints when 33% (81) and 66% (172) of events have been adjudicated (see interim analysis section below). The DSMB will be chaired by an academic cardiologist who is an expert in TAVI care and statistical analyses in clinical trials.

STUDY SCHEDULE

- **SCREENING:** During hospitalization for TAVI.
- **ENROLLMENT/BASELINE.** At discharge, randomization will take place and baseline patient data will be recorded. The investigator must ensure that the patient signs the informed consent, meets the inclusion criteria and has no exclusion criteria.
- **OPEN-LABEL TREATMENT PHASE:** 2 years.
    - FOLLOW-UP. At 3±1 and 12 months. Clinical follow-up (telephone and medical history revision) will be performed to detect any potential event (end-points and adverse events). To report data about echocardiography and laboratory tests during the first year will be optional
    - FINAL FOLLOW-UP. 1 year after last patient enrolment. All patients underwent 12 months follow-up.
    - EARLY TERMINATION VISIT. In case the patient leaves the study ahead of time (due to personal decision), a clinical follow-up (telephone and medical history) will be performed at the time of leaving the study.

	SCREENING During admission	ENROLLMENT At discharge	OPEN LABEL TREATMENT STRATEGY After discharge Month 3±1	 Month 12
Administrative data				
Inclusion/exclusion criteria	X			
Informed consent		X		
Demographic		X		
Clinical data				
Medical history		X		
Data about TAVI		X		
Physical examination		X		
Medication history		X		
ECG		X	X*	
Echocardiography		X	X*	
Laboratory data		X	X*	
Medication at discharge		X		
Drug (dapagliflozin yes/no)				
Randomization		X		
Follow-up				
Vital status			X	X
Events of end-point			X	X
Adverse events			X	X
Addition of SGLT-2 inhibitor			X	X
Discontinuation of dapafliflozin			X	X
Functional class			X	X

* Although not mandatory, researchers will be encouraged to attach ECG, echocardiograms reports, and laboratory tests data performed in the first year after TAVI.

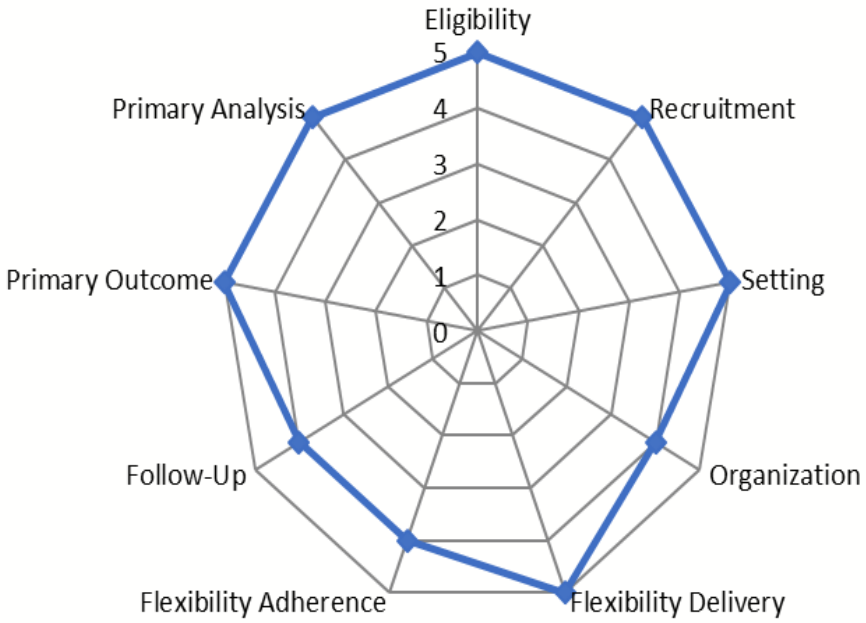
PRAGMATIC TRIAL JUSTIFICATION

STUDY DESIGN

The Dapagliflozin after Transcatheter Aortic Valve Implantation (DapaTAVI) study is a multinational, pragmatic, parallel-controlled, prospective, randomized, open-label blinded endpoint phase IV parallel- clinical trial (32).

PRAGMATIC DESIGN JUSTIFICATION

Pragmatic clinical trials are performed under normal conditions with the intention of providing results that are more applicable to clinical practice and decision making. The adequacy of the intended purpose of the DapaTAVI trial to a pragmatic design was evaluated through the nine PRECIS-2 domains (33):



1. **Eligibility** - to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?
    - Exclusion criteria are limited to formal contraindications for SGT2-inhibitors. No specific restrictions are present and inclusion criteria is extremely flexible: every patient with aortic stenosis and any degree of LVH being discharged after TAVI with prior historiy of HF or LVEF ≤ 40% is eligible (Score 5)
2. **Recruitment** - how much extra effort is made to recruit participants over and above what that would be used in the usual care setting to engage with patients?
    - Participant recruitments are performed in tertiary referral hospitals at hospital discharge. No additional resources or publicity are used to recruitment. (Score 5)
3. **Setting** - how different is the setting of the trial and the usual care setting?
    - Identical setting to usual care setting. (Score 5)
4. **Organization** - how different are the resources, provider expertise and the organization of care delivery in the intervention arm of the trial and those available in usual care?
    - Information cards are given to the participants. A telephone information system is available for participant questions. (Score 4)
5. **Flexibility (delivery**) - how different is the flexibility in how the intervention is delivered and the flexibility likely in usual care?
    - Full flexibility, dapagliflozin 10 mg once a day (Score 5)
6. **Flexibility (adherence)** - how different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care?
    - Patients receive usual encouragement to adhere to the intervention. Medical care providers are encouraged to maintain treatment unless a new clear clinical indication is present. No other measures to improve compliance. (Score 4)
7. **Follow-up** - how different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care?
    - Participants are followed as usual care except for 3 additional phone contacts during the follow-up period. (Score 4)

8. **Primary outcome** - to what extent is the trial's primary outcome relevant to participants?
    - The primary outcome is a composite of hard clinically meaningful endpoints: mortality or HF admission. (Score 5)
9. **Primary analysis** - to what extent are all data included in the analysis of the primary outcome?
    - Primary analysis is performed applying the intention-to-treat principle in the full dataset, no matter whether compliance. (Score 5)

DATA ANALYSIS SET

- **Full Analysis Set:**

  In this document, the term full analysis set is used to describe the analysis set which is as complete as possible and as close as possible to the intention-to-treat ideal of including all randomized subjects. Participants who fail to satisfy an entry criterion (eligibility violations) will be excluded from this dataset. In order not to introduce bias, the following circumstances have to apply:

  - The entry criterion will be measured prior to randomization.
  - The detection of the relevant eligibility violations will be made completely objectively.
  - All detected violations of the particular entry criterion will be excluded.

- **Per Protocol Set:**

  The per protocol set is the subset of the subjects in the full analysis set without treatment crossovers. In this data set, participants who switch from their randomized treatment will be therefore censored at the time of their switch.

RANDOMIZATION

Randomization will be performed centrally via a web or dedicated mobile application. Randomization will follow a permuted-block design with varying block sizes to ensure the continued equivalence of each group size and will be estratified according to center.

STATISTICAL PLAN: SAMPLE SIZE CALCULATION, ADAPTIVE DESIGN, INTERIM ANALYSES

SAMPLE SIZE

The number of subjects was determined for the primary endpoint of the trial.

- **Assumptions:**
  - Overall alpha value: 0.05
    - Haybittle-Peto approach for interim monitoring
      - 1st interim analysis: alpha value of 0.001
      - 2nd interim analysis: alpha value of 0.001
      - Final analysis: alpha value of 0.05
  - Power: 0.80.
  - Test: log-rank (superiority – two-sided)
  - Minimal treatment effect: HR 0.70.
  - 1-year incidence of primary endpoint (controls): 30%
  - Accrual period: 2 years
  - Follow-up period: 1 year for all patients.
  - Percentage of subjects anticipated to withdraw: 5%
- **Number of expected primary endpoints:** 260.
- **Sample size:** 1,020 participants

ADAPTIVE SAMPLE SIZE: The sample size for this study was based on the anticipated incidence of the composite endpoint. It is anticipated that the 1-year incidence of the primary endpoint will be 30% in the control arm and 21% in the dapagliflozin arm (thus, 25.5% in the overall population). To reduce the chances of having an underpowered study secondary to an event rate lower than predicted, a blinded examination of the study overall event rate will be done 3 months before closing the recruitment. At that moment, it is anticipated that >400 patients already underwent 12 months follow-up. In the case that the overall event rate is below 25%, the DSMB will discuss the possibility to doing a re-calculation of sample size according to actual event rate, and the chair will decide if it is needed to increase sample size (thus

extend recruitment period). As this analysis will be performed in a blinded fashion, adjustment for multiplicity is not required and will not be applied.

INTERIM ANALYSIS

Two interim analyses will be performed on primary endpoint and secondary safety endpoints when 33% (86) and 66% (172) of events have been adjudicated. Efficacy and safety interim analyses will be performed following the same methodological guidelines described in this document for the final analysis. Stopping rules for efficacy analysis will be based on the statistical Haybittle-Peto approach, with an overall alpha value 0.05. Safety analyses will be addressed by applying descriptive statistical methods to the data, supplemented by calculation of confidence intervals. No formal statistical stopping rules for safety data will be predefined.

REDUCING BIAS

- **Randomization:**

  Randomization introduces a deliberate element of chance into the assignment of treatments to subjects in a clinical trial. In this trial, randomization procedure is organized centrally, and it is characterized by being stratified by center and follows a permuted-block design with varying block sizes to reduce predictability of the random sequence.

- **Blinding:**

  As this trial follows a PROBE design, open-label and blinded endpoint adjudication are intrinsic characteristics. Masking is no implemented for patient and care provider. Therefore, to reduce potential bias, the endpoint adjudication panel remains blinded to treatment allocation and hard clinical meaningful endpoints have been selected as primary endpoint.

- **Multiplicity:**

Multiplicity can raise concerns regarding type I error. To address multiplicity problems, two strategies are implemented. First, a composite endpoint is selected as primary endpoint. Second, Haybittle-Peto approach is applied to account for interim analyses.

- **External validity:**
  The pragmatic design of this trial, as evaluated through PRECIS-2 guidelines, increases the generalizability of its conclusions to real daily clinical practice.

DESCRIPTIVE ANALYSIS

The distribution of continuous variables will be analyzed with graphical methods. For normally distributed variables, results will be expressed as mean ± SD; otherwise they will be represented as median (first quartile to third quartile). Categorical variables will be expressed as absolute frequency (%). Significance testing of baseline differences between treatment groups will be not performed.

PRIMARY ANALYSIS

Primary analyses will be performed in the "full data set" in an intention-to-treat fashion. The intervention arm will be compared against the control arm for the composite primary endpoint. Time-to-event will be evaluated using the Kaplan-Meier survival analysis followed by multivariable Cox proportional hazards model. Hazard ratios (HR) with corresponding 95% confidence intervals will be calculated for treatment effect estimation. All patients without an event will be censored at last day of follow-up. Patients that withdraw from follow-up will be considered censored on the day of withdrawal. Due to the randomization process and the large sample size of the trial, it will be not expected the presence of covariate relevant imbalances between treatment groups. However, for exploratory purpose, standardized differences will be calculated. Those known prognostic factor presenting an imbalance higher than 0.1 standardized difference will be included in the multivariable Cox model. For all tests, we will use 2-sided p-values with alpha ≤0.05 level of significance.

SECONDARY ANALYSIS

The secondary endpoints will be the individual components of the primary composite endpoint, besides CV mortality and the development of new atrial fibrillation. Analyses will be performed following the same guidelines described for primary analysis. Multiplicity adjustment will be not implemented because the hierarchical structure between primary and secondary endponits.

To better explore the treatment effect under ideal circumstances (explanatory approach), primary and secondary endpoint analyses will be replicated in the "per protocol data set" using same methods described above.

SUBGROUP ANALYSIS

All subgroup analyses will be performed using interaction models based on the primary analysis model, also including the subgroup in question and the treatment-subgroup interaction as factors, and presented as treatment hazard ratios for each subgroup and the interaction p-value. Subgroups will be specified in the endpoints section below.

PRE-SPECIFIED SUB-GROUP ANALYSES

- Diabetic vs non-diabetic patients.
- LVEF ≤ vs > 40%.
- ≥ 80 years vs < 80 years of age on recruitment
- Males vs females
- Atrial fibrillation versus sinus rhythm
- Hypertensive vs normotensive patients
- Moderate-severe vs mild LVH.
- Treatment with beta-blockers vs. no beta-blockers

- Treatment with renin-angiotensin system blocking drugs vs no renin-angiotensin system blocking drugs.

ETHICS/PROTECTION OF HUMAN SUBJECTS

ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the Institutinal Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any

procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study

PARTICIPANT AND DATA CONFIDENTIALITY

Participant confidentiality is strictly held in trust by the participating investigators and the sponsor. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor. The study monitor, other authorized representatives of the sponsor, or representatives of the IRB, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study data entry and study management systems used by clinical sites, by the coordinating center, and research staff, will be secured and password protected. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all study databases will be de-identified and archived at the Instituto de Investigacion Sanitaria Galicia Sur, for as long a period as dictated by local IRB and Institutional regulations. Individual participants and their research data will be identified by a unique study identification number.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose

information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

DATA HANDLING AND RECORD KEEPING

DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into the data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after completing the study. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the consent of the sponsor. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained

PROTOCOL DEVIATIONS

It is the responsibility of the site to use continuous vigilance to identify and report protocol deviations, defined as any noncompliance with the clinical trial protocol. Protocol deviations must be sent to the local IRB. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

PUBLICATION AND DATA SHARING POLICY

According to the clinical trials registration policy of the International Committee of Medical Journal Editors (ICMJE) member journals, the DapaTAVI trial will be registered in a public trials registry such as EUDRA and ClinicalTrials.gob, which is sponsored by the National Library of Medicine.

Study design will be presented in a scientific publication.

The results will be submitted to peer-reviewed journal fulfilling the ICMJE guidelines, ensuring that the public has access to the published results.

STUDY ADMINISTRATION

STEERING COMMITTEE

The Steering Committee will govern the conduct of the study. The Steering Committee is responsible for making decisions, endorsing executive committee actions, and providing advice.

EXECUTIVE COMMITTEE

The executive committee is responsible to implement the actions of the trial and to assure the trial is conducted according to its design. The executive committee is responsible for the daily operations of the trial.

DATA SAFETY MONITORING BOARD (DSMB)

The DSMB is a group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing. The primary mandate of the DSMB is to protect patient safety. If adverse events of a particularly serious type are more common in the experimental arm compared to the control arm, then the DSMB would have to strongly consider termination of the study.

CLINICAL EVENTS COMMITTEE

The clinical events committee is responsible for evaluating the information provided regarding a potential event and adjudicate events according to the trial protocol. This committee is blinded to treatment allocation. Information collected will be blinded and any comment related to treatment allocation will be eliminated before the committee has access to this information.

CONFLICT OF INTEREST POLICY

The DapaTAVI trial is an independent, investigator-initiated and investigator-led, multicentre, randomised trial. Any actual conflict of interest of persons who have a role in the design conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.

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