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Dapagliflozin in patients with stable coronary heart disease

Submission date
24/11/2023

Recruitment status
Recruiting

Registration date
04/12/2023

Overall study status
Ongoing

Last Edited
03/08/2026

Condition category
Circulatory System

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Ischemic preconditioning (IP) is recognized as a protective cellular mechanism in which brief, recurrent episodes of myocardial ischemia followed by reperfusion can self-protect the heart from prolonged ischemic injury and thereby limit myocardial infarction size. Despite its cardioprotective profile demonstrated by numerous clinical studies, the results of studies on the action of SGLT2 inhibitors (dapagliflozin) in IP are scarce. The few studies that have addressed this question have been carried out in animal models. Furthermore, in humans, there are no studies that have evaluated the effects of dapagliflozin on IP expression. Thus, the objective of the present study is to evaluate IP in patients with symptomatic coronary artery disease (CAD) and preserved ventricular function, and to evaluate whether dapagliflozin influences this important myocardial protection mechanism.

Who can participate?
Patients aged between 18 and 80 with chronic coronary obstructions and preserved cardiac function and able to undergo an exercise stress test

What does the study involve?
The study involves performing 2 treadmill exercise tests with a 30-minute interval between them. If the presence of myocardial ischemia is detected, participants will receive dapagliflozin at a dose of 10mg once a day for 7 days. They will then perform another 2 treadmill exercise tests with a 30-minute interval between them. Usual medications, such as beta-blockers, calcium channel blockers, nitrates, and other oral hypoglycemic agents, must be suspended for 1 week before each test.

What are the possible benefits and risks of participating?
The main benefit of this study is a possible improvement in myocardial ischemia with the use of dapagliflozin. The risks of this study include those related to the procedures performed and the momentary suspension of some medications commonly used by the patient. The main complications of exercise testing are hypertension, cardiac arrhythmias, such as atrial fibrillation (irregular heart rhythm), prolonged chest pain and unstable angina.

Where is the study run from?
Instituto do Coração (InCor) (Brazil)

When is the study starting and how long is it expected to run for?
May 2022 to May 2027

Who is funding the study?
Instituto do Coração (InCor) (Brazil)

Who is the main contact?
Thiago L Scudeler, thiago.scudeler@fm.usp.br

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Additional identifiers

Study information

Scientific Title
Role of dapagliflozin in ischemic preconditioning in patients with symptomatic coronary artery disease

Acronym
DAPA-IP

Study objectives
Dapagliflozin improves ischemic preconditioning in patients with stable coronary artery disease and preserved left ventricular function

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 24/11/2022, Comitê de Ética e Pesquisa do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (Rua Ovídio Pires de Campos, 255, Sao Paulo, 05.403-010, Brazil; +55(11)2661-7585; cappesq.adm@hc.fm.usp.br), ref: 65199022.4.0000.0068

Primary study design
Interventional

Study design
Prospective interventional single-center study

Study type(s)
Efficacy

Health condition(s) or problem(s) studied
Patients with documented multivessel coronary artery disease, documented ischemia by stress testing and preserved left ventricular ejection fraction (LVEF)

Interventions
Ischemic preconditioning (IP) is a powerful cellular protection mechanism. The cellular pathways underlying IP are extremely complex and involve the participation of cell triggers, intracellular signaling pathways, and end-effectors. Experimental studies have shown that sodium-glucose transport protein 2 (SGLT2) inhibitors promote activation of 5-adenosine monophosphate (AMP)-activated protein kinase (AMPK), the main regulator of adenosine 5-triphosphate homeostasis and energy metabolism in the body. Despite its cardioprotective profile demonstrated by numerous clinical trials, the results of studies on the action of SGLT2 inhibitors in IP are scarce. This study investigates the effects of dapagliflozin on IP in patients with coronary artery disease (CAD).

Briefly, patients will undergo 4 exercise tests, the first two, with a time interval of 30 minutes between them, after the washout period of cardiovascular or hypoglycemic medications and, the last two, after 7 days of dapagliflozin 10 mg once a day, also with a time interval of 30 minutes between them.

Patient preparation
After clinical and cardiological evaluation, patients will be instructed to stop medications with

cardiovascular effects before sequential exercise tests, depending on the half-life of the drug. Diabetic patients will be instructed to suspend medications with cardiovascular effects and oral hypoglycemic agents for a similar period before the tests. Only nitrates will be maintained, when necessary, up to 24 hours before testing. Patients will be instructed not to perform physical activities during the test period, to control their salt intake and patients with diabetes will be advised to strictly control their carbohydrate intake. They will also be instructed to contact the study team by telephone, who will be available 24 hours a day, in case of questions or worsening of symptoms. On the day of the exams, the symptoms will be reassessed by the medical team before carrying out the sequential exercise tests.

Sequential ergometric tests
The study protocol will include 2 phases. In Phase 1, after the washout period of cardiovascular or hypoglycemic medications, all patients will undergo 2 consecutive Exercise Treadmill Tests (ETT) [ETT1 and ETT2], with a 30-minute interval between them to identify the ischemia and document the magnitude of IP by the difference in ischemia parameters between the 2 tests. The protocol will be adopted according to the assessment of each patient's functionality (Bruce or modified Bruce). The ergometer used will be the GE T2100 Ergometric Treadmill coupled to the GE Case V6.73 system/software and the Tango M2 blood pressure monitor.

The recording system used will be 12 leads, including the classic leads of the Mason and Likar systems. Electrocardiographic recordings will be carried out in a standardized way, pre-exertion, every 5 to 10 seconds at a time close to T-1.0 mm, at the peak of exercise, at the time of the worst electrocardiographic change, at the time of arrhythmias and every minute of the recovery, which will last for 6 minutes. Exercise tests that result in depression of the ST segment during effort greater than or equal to 1.0 mm, horizontal or descending, associated or not with chest pain will be considered positive. Heart rate will be continuously monitored and documented every 15 seconds. Blood pressure measurement will be performed every 90 seconds, at the moment of T-1.0 mm, at peak effort and every minute of the recovery phase. The double product or rate pressure product (RPP) will be calculated by multiplying the heart rate in beats per minute (bpm) by the blood pressure in millimeters of mercury (mmHg), this variable being measured at the time of T-1.0 mm. The criteria for interrupting exams will be those adopted by the recommendations of the Brazilian Society of Cardiology Guidelines.

After Phase 1, all patients will receive dapagliflozin at a dose of 10mg once a day for 6 days. On the seventh day, patients will receive dapagliflozin 10mg and will again undergo 2 consecutive ETTs (ETT3 and ETT4) 2 hours after medication administration (time to reach peak plasma concentration) [Phase 2]. The time interval between ETT3 and ETT4 will be similar to that of phase 1, that is, 30 minutes.

Only experienced cardiologists will participate in this study protocol. They are: 1 cardiologist specializing in ergometry and 2 clinical cardiologists.
The study medication, dapagliflozin, will be delivered in person, at the Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo, to each participant individually (face-to-face). The intervention is taking place at Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo, a public, university hospital, which serves highly complex patients. The hospital is located in São Paulo and supports cardiovascular surgery and hemodynamics.

Intervention Type
Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)
Dapagliflozin

Primary outcome(s)
Time required to achieve 1.0 mm of ST segment depression (T-1.0 mm) measured using the treadmill ECG stress test at baseline without dapagliflozin and 7 days with dapagliflozin

Key secondary outcome(s)
1. Heart rate pressure product (RPP) measured using the treadmill ECG stress test at baseline without dapagliflozin and 7 days with dapagliflozin
2. Improvement of angina measured using the treadmill ECG stress test at baseline without dapagliflozin and 7 days with dapagliflozin

Completion date
15/05/2027

Eligibility

Key inclusion criteria
1. Stable multivessel coronary artery disease (obstruction greater than 70% in at least 2 main coronary branches).
2. LVEF ≥0.50, confirmed by transthoracic Doppler echocardiography.
3. Documentation of stress-induced myocardial ischemia (horizontal or descending ST segment depression ≥ 1.0 mm)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
80 Years

Sex
All

Total final enrolment
0

Key exclusion criteria

1. Kidney failure (creatinine clearance < 60 ml/min)
2. Severe liver failure
3. Single-vessel coronary artery disease
4. Myocardial infarction in the last 3 months
5. LVEF < 50%
6. Presence of any non-ischemic cardiomyopathy
7. Moderate or severe valve disease
8. Morphological changes in the qrs of the ecg and conduction defects that may interfere with the interpretation of changes in the st segment
9. Recent and negative exercise test for myocardial ischemia
10. Positive exercise test for myocardial ischemia, with signs of high risk
11. Limiting anginal symptoms or recent worsening
12. Arrhythmias that make it difficult to characterize myocardial ischemia during exercise stress (atrial fibrillation or flutter)
13. Patient refusal to participate in the study

Date of first enrolment
15/12/2022

Date of final enrolment
15/05/2027

Locations

Countries of recruitment
Brazil

Study participating centre
Instituto do Coração (InCor)
Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
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Sponsor information

Organisation
Instituto do Coração

ROR
https://ror.org/04x2nj883

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Instituto do Coracao

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from Thiago L Scudeler, thiago.scudeler@fm.usp.br. All individual participant data collected during the trial will be shared, after identification, immediately following publication. Consent will be obtained from all participants. All participant data will be kept anonymous, as detailed in the informed consent. The Research Ethics Committee will supervise all stages of research at the Instituto do Coração do Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		10/07/2024	03/09/2024	Yes	No