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# SGLT2i Dapagliflozin in primary prevention of chemotherapy induced cardiotoxicity in breast cancer patients treated with neo-adjuvant anthracycline-based chemotherapy +/- trastuzumab: rationale and design of the multicenter PROTECT trial

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## Abstract

**Background** SGLT2i exerts several cardiometabolic benefits in heart failure with reduced and preserved ejection fraction through the systemic reduction of insulin, visceral fat, chemokines and growth factors involved in cardiovascular diseases. Anthracyclines are considered the principal culprit drugs behind chemotherapy-induced cardiotoxicity. The pathognomonic manifestation of anthracycline-induced cardiotoxicity is a hypokinetic cardiomyopathy progressively leading to heart failure. Anthracycline-induced cardiotoxicity is still a significant problem that compromises the quality of life and overall survival of breast cancer (BC) patients. Sequential therapy regimen of anthracyclines and HER-2 blocking agents is associated to higher risk of cardiotoxicity compared to monotherapy regimen. Recent studies in preclinical models of anthracycline-induced cardiotoxicity concluded that SGLT2i are able to prevent ejection fraction reduction and myocardial inflammation and fibrosis. A very recent retrospective study indicates that SGLT2i were associated with lower rate of cardiac events among patients with cancer and T2DM who were treated with anthracyclines. These data support the conducting of a randomized clinical trial testing Dapagliflozin in patients with breast cancer treated with anthracyclines+/- trastuzumab.

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**Objective** To evaluate the cardioprotective effects of the SGLT2 inhibitor Dapagliflozin in chemotherapy-naive patients with stage I–III breast cancer undergoing anthracycline-based treatment with or without trastuzumab, by assessing its ability to reduce the incidence of cardiotoxicity and improve systemic cardiometabolic markers.

**Methods** Chemotherapy-naive patients (18–70 years) scheduled for antracycline +/- trastuzumab treatment in the [neo-]adjuvant setting for stage I-III breast cancer, will be randomized using a web-based system stratified by the use of trastuzumab to follow a chemotherapy regimen plus Dapagliflozin [10 mg/die] [active group] or chemotherapy regimen plus standard of care [control group]. During follow up period, if a patient develops asymptomatic or symptomatic systolic disfunction will be treated according to good clinical practice. From randomization, to the third, sixth, twelfth and eighteenth months, echocardiographic and cardiological visits will be performed associated to blood analysis for quantification of cardiotoxicity biomarkers (NT-pro-BNP, hsTNI), CKD-EPI eGFR and systemic inflammation (hsCRP, chemokines, cytokines and growth factors).

**Results** The study is ongoing. Results will be published when the study is completed.

**Conclusion** The PROTECT trial is the first randomized clinical study designed to evaluate whether Dapagliflozin can reduce anthracycline- and/or trastuzumab-associated cardiotoxicity in patients with early-stage breast cancer. Beyond its established cardiometabolic effects, this trial will also provide insight into the systemic anti-inflammatory and metabolic benefits of SGLT2 inhibition in the oncology setting. Findings from this study may pave the way for novel cardio-oncology strategies aimed at improving both cardiac outcomes and quality of life in cancer patients.

**Trial registration** ClinicalTrials.gov NCT06341842 [EudraCT Number 2022-003377-28]. Registered on 19 March 2024.

**Keywords** Cardiovascular disease, Risk factors, Beast cancer, Cardio-oncology, Inflammation, Metabolism, Trastuzumab

## Background

Despite improved survival of patients with cancer, chemotherapy has also increased morbidity and mortality due to treatment side effects [1]. Anthracyclines (AC) are among the most widely used chemotherapeutic agents and have been shown to be effective in a wide range of tumors, in particular breast cancer. Their clinical effectiveness, however, may be thwarted by the development of cardiotoxicity that negatively affects patients' outcomes and seriously limits their oncological therapeutic opportunities [2]. Anthracyclines are associated with a dose dependent cardiotoxicity [1]. Cancer patients treated with anthracyclines at 400 mg/m2 and 700 mg/m2 are exposed to a 5% and 48% risk of congestive heart failure. Mechanisms of acute and chronic anthracyclines-mediated adverse events involves ferroptosis, endothelial damages, apoptosis, fibrosis and myocardial inflammation mediated by overexpression of NF-kB mediated pathways. Notably, short-term induced myocardial damages due to doxorubicin are well reported in the clinical scenario, resulting in the need of cardioprotective strategies in primary prevention in patients with cancer. Cardiotoxicity from combination therapies is a clinical problem of extreme significance in oncology; a relevant example is the additive cardiotoxicity from the combination of anthracyclines and trastuzumab in HER2 + breast cancer. The cumulative [adjusted] incidence of adverse cardiac events in women treated with anthracyclines and trastuzumab 1 year after diagnosis of breast cancer is 16.4%, 23.8% after 2 years and at 3 years 28.2% [3–10]. Based on these data, as well as on the limited clinical effectiveness of conventional cardiovascular drugs (e.g. beta-blockers and RAAS inhibitors), the discovery of new cardioprotective agents in these patients could be of key importance to avoid discontinuation or interruption of anticancer therapies thus increasing overall survival.

In the last twenty years several randomized and observational trials tried to study a prophylactic intervention in order to avoid drug-induced cardiotoxicity and the onset of heart failure [11–14]. A meta-analysis published in 2019 evaluated 15 RCT investigating the efficacy of neurohormonal drugs in preventing cardiovascular toxicity in patients receiving chemotherapy [15]. This meta-analysis showed a significant, but small, benefit of neurohormonal therapies in reducing decline in LV systolic function among patients undergoing chemotherapy. However, owing to the substantial heterogeneity across the modest-sized studies, its findings are not sufficient to recommend routine use of RAAS inhibitors or beta-blockers as cardioprotective strategies in patients undergoing chemotherapy.

Sodium Glucose-Cotransporter Type 2 inhibitors (SGLT2i) have beneficial properties, including the improvement of systolic and diastolic functions, increases in calcium homeostasis, reduction of afterload and oxidative stress, improvement of mitochondrial functions in cardiomyocytes, increases in ketone bodies, overall resulting in an improved energy metabolism of cardiac cells, reduction of insulin and uric acid levels as well as of epicardial and visceral fat [16–20] (Fig. 1).

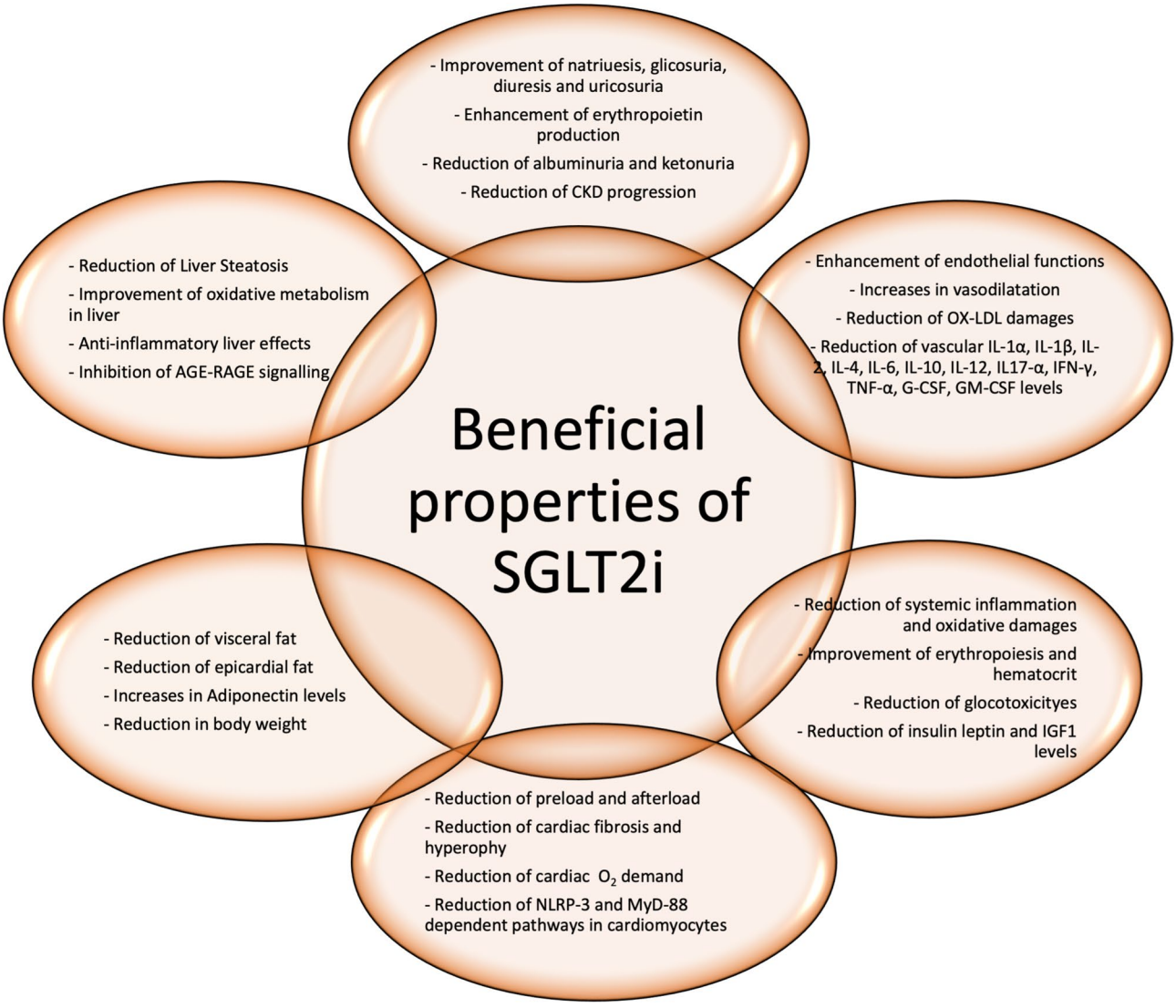


**Fig. 1** beneficial properties of SGLT2i

Dapagliflozin (DAPA) is a selective SGLT2 inhibitor with multiple beneficial properties in patients with cardiovascular diseases (CVD) [21–23]. In DAPA-HF TRIAL [21], DAPA reduced heart failure and death from cardiovascular causes in patients with heart failure and reduced ejection fraction in patients with and without T2DM. In DEFINE-trial, DAPA improved heart failure-related health status and reduced natriuretic peptides in patients with heart failure with reduced ejection fraction [22]. In DELIVER trial, in patients with heart failure and preserved ejection fraction, DAPA reduced significantly cardiovascular death and urgent heart failure visit in patients with T2DM [23]. A very recent retrospective study in T2DM cancer patients treated with anthracyclines, gliflozins reduced heart failure admissions, new cardiomyopathies, arrhythmias and heat failure incidence [24]. Dapagliflozin could have high potential to prevent anthracyclines-mediated cardiotoxicity in cancer patients without diabetes through its cardio-renal benefits [25]–[26]. To our knowledge no trial has evaluated the beneficial effects of Dapagliflozin in a specific set of patients treated with [neo-] adjuvant Anthracycline-based chemotherapy +/- trastuzumab.

## Methods

### Study design and objectives

PROTECT trial is a phase II "proof of concept", multicentre, randomized 1:1, open label, parallel-groups study, designed to evaluate if dapagliflozin reduces chemotherapy-induced cardiotoxicity (CTRCD) in participants with breast cancer treated with [neo-] adjuvant Anthracycline-based chemotherapy +/- trastuzumab. The study aims to describe an efficacy for dapagliflozin compared to standard of care.

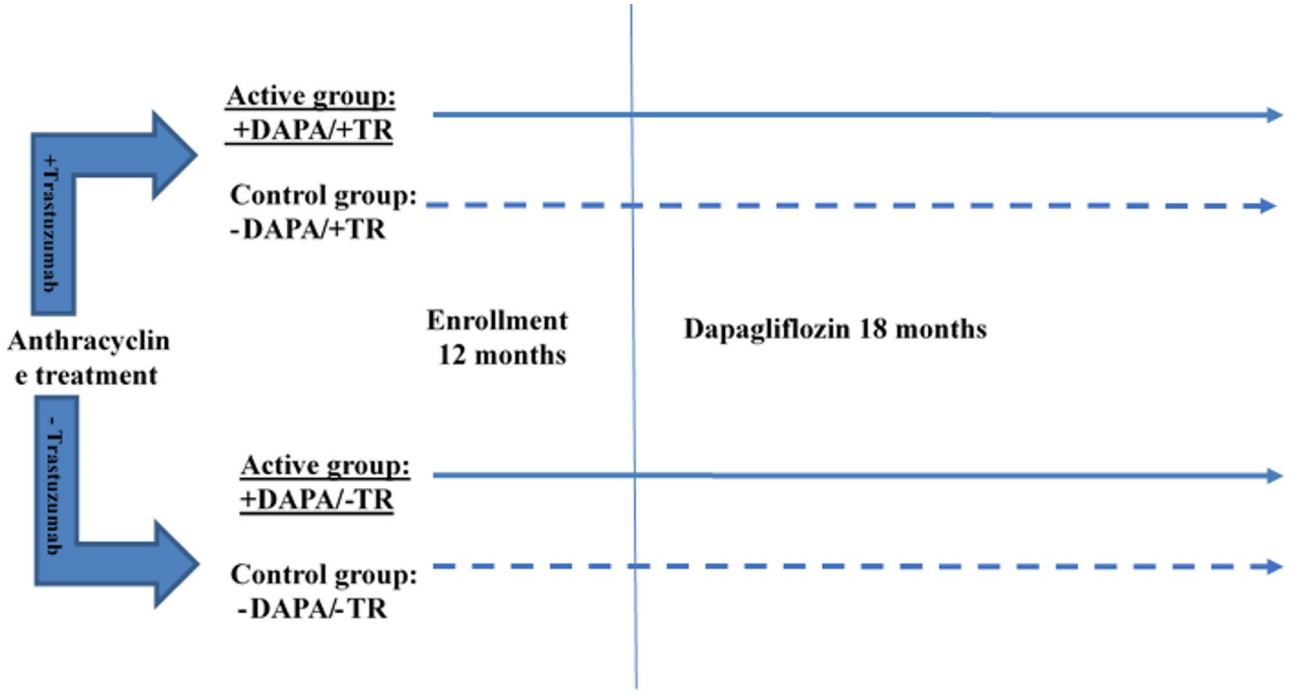


**Fig. 2** Schematic representation of the study design showing anthracycline treatment, enrollment period (12 months), and follow-up with dapagliflozin treatment for 18 months in active (+DAPA/+TR) and control (–DAPA/+TR) groups

**Table 1** List of participating centers

| Center | Role | PI |
|---|---|---|
| Fondazione IRCCS Policlinico San Matteo – Pavia | Coordinator | Laura Scelsi |
| Istituto Nazionale Tumori - IRCCS - Fondazione "G.Pascale" - Napoli | Participant | Nicola Maurea |
| Ospedale "Guglielmo da Saliceto" - Piacenza | Participant | Andrea Tedeschi |
| Ospedale Universitario delle Marche - Ancona | Participant | Francesco Guerra |
| Ospedale Versilia – Lido di Camaiore | Participant | Maria Laura Canale |
| IRCCS Istituto Tumori "Giovanni Paolo II" - Bari | Participant | Stefano Oliva |
| Ospedale Alessandro Manzoni - Lecco | Participant | Giuseppe Uccello |

The study design is shown in Fig. 2.

The study involves seven cancer centers in Italy (Table 1) and it started on November 2023.

This study was approved by the ethic board of the Italian Medicine Agency (AIFA), and of each recruiting hospitals, such as EudraCT Number 2022-003377-28. The study has been registered with ClinicalTrials.gov [registration date and number: 2024-03-19 and NCT06341842].

The new 2022 ESC Cardio-Oncology Guidelines [10] classified CTRCD in:

Asymptomatic CTRCD.

- Severe: New LVEF reduction to < 40%.
- Moderate: New LVEF reduction by ≥ 10% points to an LVEF of 40–49% OR New LVEF reduction by < 10% points to an LVEF of 40– 49% AND either new relative decline in GLS by > 15% from baseline OR new rise in cardiac biomarkers [cTnI/cTnT > 99th percentile, BNP ≥ 35 pg/mL, NT-proBNP ≥ 125 pg/mL or new significant rise from baseline beyond the biological and analytical variation of the assay used.]
- Mild: LVEF ≥ 50% AND new relative decline in GLS by > 15% from baseline AND/OR new rise in cardiac biomarkers [cTnI/cTnT > 99th percentile, BNP ≥ 35 pg/mL, NT-proBNP ≥ 125 pg/mL or new significant rise from baseline beyond the biological and analytical variation of the assay used).

Symptomatic CTRCD: represents HF, which is a clinical syndrome consisting of cardinal symptoms [e.g. breathlessness, ankle swelling, and fatigue] that may be accompanied by signs [e.g. elevated jugular venous pressure, pulmonary crackles, and peripheral oedema] and has traditionally been divided into distinct phenotypes based on the measurement of LVEF: ≤40%= HFrEF; 41–49%=HFmrEF; ≥50%=HFpEF.

The purpose of this study is to evaluate whether dapagliflozin reduces chemotherapy induced cardiotoxicity in participants with breast cancer treated with [neo-]adjuvant anthracycline-based chemotherapy +/- trastuzumab.

The study seeks primarily to assess whether the administration of dapagliflozin is associated with a lower rate of asymptomatic and symptomatic CTRCD during 18 months. The key co-primary objective is to assess whether the administration of dapagliflozin is associated with a lower rate of asymptomatic CTRCD during 18 months.

The primary and key secondary outcome will be measured using transthoracic echocardiography and cardiac biomarkers. For this purpose we calculate during transthoracic echocardiography LVEF [%] and GLS [%], according to definition of CRTCD in ESC Cardio-Oncology Guidelines [10].

The study secondary objectives will be: 1] Difference in severe, moderate and mild asymptomatic CTRCD between the two groups during 18 months according to the background therapy with AC with or without TZ and with or without the use of any of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or beta-blockers for their potential cardioprotective role on cardiotoxicity development [subgroup analysis] [11–15]; 2] Difference in symptomatic CTRCD between the two groups during 18 months according to the background therapy with AC with or without TZ [subgroup analysis] 3] Change from baseline of at least of one grade of diastolic disfunction [according to ESC guidelines [27], Appendix 1] during 18 months. 4] Change from baseline in end diastolic and systolic left ventricular volumes and in left atrial volume during 18 months. 5] Change in plasma levels of the bio-humoral markers between baseline and follow-up at three, six, twelve and eighteen months: • NT-pro-BNP • hsTNI • CKD-EPI eGFR • hsCRP.

The safety outcome include: decline in eGFR under 25 ml/min/1.7 mq; documented clinical hypoglycaemic events; premature interruption of trial drug due to recurrent genito-urinary tract infections; premature interruption of trial drug due to symptomatic hypotension; cancer relapse; new cancer events.

### Participants

We will consider all consecutive chemotherapy-naive patients, scheduled for ACT +/- trastuzumab treatment for stage I-III breast cancer. These patients will be referred to Cardiology Unit by Hospital Oncologists.

### Inclusion criteria

1. Chemotherapy-naive patients scheduled for antracycline +/- trastuzumab treatment in the [neo-] adjuvant setting for stage I-III breast cancer.
2. Adult women between 18 and 70 years of age.
3. eGFR > 25 ml/min/1.7 mq.
4. ECOG score 0–2.
5. Consent form signed.
6. Female patients of childbearing potential [not surgically sterilized and between menarche and 1 year post menopause] must have a negative result from a serum pregnancy test performed within 7 days of randomization and on the day of first study treatment prior to the initiation of study treatment. Women of childbearing potential must agree to use highly effective contraceptive measures from the time of informed consent through 7 months after last dose of study drug. [More detailed information in the Sect. 7.1 of the protocol].

### Exclusion criteria

1. Left ventricular ejection fraction [LVEF] < 53%.
2. Valvular heart disease.
3. Previous malignancy requiring treatment with anthracyclines or chest radiotherapy.
4. Life expectancy ≤ 12 weeks.
5. Currently pregnant [confirmed with positive pregnancy test performed from − 7 to -1 days prior to start study drug] or unwilling to adopt highly effective contraceptive method.
6. Currently breast-feeding women.
7. History of hypersensitivity to dapagliflozin or any of the excipients of the product.
8. History of Diabetic Ketoacidosis [DKA] requiring medical intervention [e.g. emergency room visit and/or hospitalization] within 1 month prior to enrolment visit.
9. Type 1 diabetes mellitus.

### Interventions

The eligible patients who voluntarily sign the consent form will be randomized using a web-based system stratified by the use of trastuzumab to:

- Active group: chemotherapy regimen plus dapagliflozin [10 mg/die].
- Control group: chemotherapy regimen plus standard of care.

During follow up period, if a patient develops asymptomatic or symptomatic systolic dysfunction should be treated according to good clinical practice.

**Table 2** Schedule of cardiovascular parameter assessments, medical history collection, clinical procedures, laboratory tests, and safety evaluations across different study visits (screening, baseline, treatment, and end-of-trial phases)

| **Cardiovascular parameters** | **Screening** | **Basal - randomization (prior CT)** | | **Treatment period (during and post-CT)** | | **End of trial** |
|---|---|---|---|---|---|---|
| Visit | ***V1*** | ***V2*** | ***V3*** | ***V4*** | ***V5*** | ***V6*** |
| Days | -30 to -1 | -5 to -1 | 90 +/- 6 | 180 +/-6 | 360 +/- 6 | 540 +/-6 |
| Informed Consent | X | | | | | |
| Examination of inclusion and exclusion criteria | X | | | | | |
| Randomization | | X | | | | |
| Medical History | X | | | | | |
| Collection Of The Following Data: | | | | | | |
| ☐ Demography | | | | | | |
| ☐ Age | | | | | | |
| ☐ Sex | | | | | | |
| ☐ Height | | | | | | |
| ☐ Weight | | | | | | |
| ☐ Evaluation Of Any Previous Reported Allergy | | | | | | |
| ☐ Cardiovascular Risk Factors* | | | | | | |
| ☐ Oncological History, Any Other Chemo-Radiotherapy Administered In The Past Medical History | | | | | | |
| ☐ Other Comorbidities | | | | | | |
| A warning collection of the whole patient's past medical history | | | | | | |
| Clinical Procedures | X | | X | X | X | X |
| ☐ Physical Examination | | | | | | |
| ☐ Height | | | | | | |
| ☐ Weight | | | | | | |
| ☐ Pressure Arteriosue | | | | | | |
| ☐ Heart Rate | | | | | | |
| Twelve-Lead Electrocardiogram | | | | | | |
| Blood sample for laboratory tests examined in the local laboratory **: | X | | X | X | X | X |
| Transthoracic ecocardiography | X | | X | X | X | X |
| Concomitant therapy and intervention | X | | X | X | X | X |
| SAFETY EVALUATION | X | X | X | X | X | X |
| Adverse events related to the study medication | | | | | | |
| Investigational Product | | X | X | X | X | |
| Outcomes | | | X | X | X | X |
| ☐ Primary outcome | | | | | | |
| ☐ Secondary outcome | | | | | | |
| Outcome of interest | | | | | Xa | |

*Arterial Hypertension, Smoking Habits, Family History For Cardiovascular Disease, Dyslipidemia And Diabetes

** Full blood count; Creatinine; Urea; CKD-EPI; eGFR; Sodium; Potassium; GOT; GPT; Total bilirubin; Direct and indirect bilirubin; Alkaline phosphatase; Creatine Kinase [CK]; NT-pro-BNP; TNI-hs I; CRP-hs; Cytokines

Xa: post breast surgery

### Assessment measures

Evaluations will take place at baseline [Table 1], after chemotherapy and at 3-6-12-18 months.

The timing and frequency of the study visits, including assessment time windows, are presented in the table of study procedures and assessments [Table 2].

### Participant timeline

Recruitment started in October 2023 at Fondazione IRCCS Policlinico San Matteo, Pavia. Enrollment is about 12 months with follow-up period of 18 months. Total duration from first in last out is 30 months.

The data collected from the participants and the follow-up timeline are presented in Table 2.

### Sample size

The sample size is computed based on the primary endpoint and makes use of the data reported in the literature [10]. At 18 months, we expect a cumulative incidence of CTRCD of 35% in the control arm, corresponding to an event-free survival rate of 65%. With 316 patients [158 per arm] we will be able to elicit an increase in event-free survival in the dapaglifozin arm up to 80% [hazard ratio, HR 0.52, 78 events] with a power of 80 and type

I error [2-tailed] of 5%. This sample size accounts for a 10% dropout rate and the log rank test to compare event-free survivals. For calculation we used the Stata command: power log rank 0.65 0.80, wdprob[0.1] power[0.80] alpha[0.05].

#### Data management, collection and monitoring

All protocol-required information collected during the study will be entered by the investigator in the electronic case report forms (CRF). Specifically, the CRF will be based on the REDCap platform [https://projectredcap.org/]. The investigator should complete the CRF as soon as possible after information is collected. An explanation should be given for all missing data. The completed CRF will be reviewed and signed by the investigator. The main investigator will continuously monitor data.

#### Statistical analyses

All analyses will be performed using the Stata software (release 17, StataCorp, College Station, TX, USA). Continuous data will be described with the mean and standard deviation or the median and quartiles, if skewed. Categorical data will be described as counts and percent for each categories. Descriptions will be performed separately for each treatment group. A 2-sided p-value < 0.05 will be considered statistically significant. Variables may be log-transformed for the purpose of the analysis.The logrank test will be used to compare cardiac toxicity free survival. Cox regression will be used to compute HA and 95%CI. Regression models for repeated measures will be used to compare changes in biomarkers over time.

#### Research ethic approval

The study adheres to the Declaration of Helsinki on medical research protocols and ethics, the ICH-GCP as well as all national legal and regulatory requirements.

## Results

The study is ongoing. Results will be published when the study is completed.

## Discussion

Anthracycline-induced cardiotoxicity, particularly when combined with HER2-targeted therapies such as trastuzumab, represents a significant and persistent challenge in the management of early-stage breast cancer [28, 29]. Despite its well-established oncological efficacy, the cardiotoxic potential of anthracyclines can compromise long-term cardiac function, leading to asymptomatic systolic dysfunction or overt heart failure, often requiring modification or premature cessation of potentially curative cancer treatment [30]. Clinical strategies aimed at mitigating this risk have traditionally focused on early initiation of neurohormonal blockade, including ACE inhibitors and beta blockers [31, 32]. While preclinical models and observational data suggest some cardioprotective effects, randomized controlled trials in breast cancer populations have yielded mixed results, with most showing limited or no significant benefit on the preservation of left ventricular function [33].

These inconsistent outcomes may be attributed to improved contemporary chemotherapy regimens employing reduced cumulative doses of anthracyclines, better sequencing of cardiotoxic agents, and variability in trial design, including small sample sizes and heterogeneous patient populations [34].

There is a growing need for novel cardioprotective strategies that target not only hemodynamic stress but also the underlying metabolic and inflammatory mechanisms that contribute to chemotherapy-induced cardiac injury [35]. SGLT2 inhibitors, initially developed for glycemic control in type 2 diabetes, have demonstrated robust cardiovascular benefits in both diabetic and non-diabetic patients with heart failure across a range of ejection fractions [36, 37]. Their mechanisms of action extend beyond glucose excretion to include reductions in systemic insulin levels, visceral adiposity, inflammation, oxidative stress, and myocardial fibrosis, all of which are implicated in the pathogenesis of anthracycline-induced cardiotoxicity [38]. Preclinical studies in murine models of doxorubicin-induced cardiomyopathy have shown that SGLT2 inhibitors attenuate myocardial inflammation, preserve mitochondrial function, and prevent deterioration of left ventricular ejection fraction [39].

A recent retrospective cohort study provided the first clinical signal suggesting a protective role of SGLT2 inhibitors in cancer patients with type 2 diabetes undergoing anthracycline therapy, with lower rates of cardiac events observed in the SGLT2i-treated group [40]. However, prospective randomized data are lacking, particularly in patients without diabetes and in the context of HER2-directed therapies. The PROTECT trial is designed to address this gap by evaluating the cardioprotective effects of Dapagliflozin in a homogeneous population of chemotherapy-naive breast cancer patients receiving anthracyclines with or without trastuzumab. By incorporating a broad panel of biomarkers, echocardiographic parameters, and longitudinal follow-up, the trial aims to provide comprehensive insights into both functional and molecular endpoints of cardiotoxicity.

If successful, this study could redefine the standard of preventive cardio-oncology care by introducing a pharmacologic agent that not only preserves cardiac function but also improves systemic metabolic and inflammatory profiles in a high-risk oncology population.

## Conclusion

Cardio-oncology remains an evolving discipline at the intersection of two rapidly advancing fields: oncology and cardiovascular medicine. As systemic cancer therapies become increasingly effective and tailored, the spectrum of treatment-related cardiovascular complications is also expanding, necessitating a more nuanced and proactive approach to prevention and management. In early breast cancer, therapeutic strategies continue to shift with the introduction of anthracycline-sparing regimens, novel HER2-targeted agents, and biomarker-guided treatment decisions, all of which have implications for the design and interpretation of cardio-oncology trials. Consequently, data from older studies may not fully reflect the complexities of current clinical practice. To date, most pharmacologic interventions aimed at preventing cardiotoxicity have yielded limited success, often due to modest treatment effects, suboptimal timing of intervention, or inadequate mechanistic targeting.

Notably, SGLT2 inhibitors represent a promising class of agents with multimodal cardioprotective actions extending beyond hemodynamic modulation to include metabolic and anti-inflammatory effects, features particularly relevant in the setting of anthracycline-induced myocardial injury.

The PROTECT trial is specifically designed to evaluate the efficacy of Dapagliflozin in a well-characterized breast cancer population receiving cardiotoxic therapy regimen. By integrating functional imaging, biomarker surveillance, and rigorous clinical follow-up, this study seeks to generate high-quality evidence that could inform a new preventive paradigm in cardio-oncology. Should its hypotheses be confirmed, PROTECT may not only expand the therapeutic utility of SGLT2 inhibitors but also contribute meaningfully to improving long-term cardiovascular outcomes in cancer survivors.

## Appendix 1

Diastolic dysfunction will be diagnosed according to the echocardiographic examination results and categorized into 3 grades based on 2016 version of recommendations [27], that is: grade 1 [mild diastolic dysfunction or impaired relaxation phase: E/A ≤ 0.8, DT > 200 milliseconds, E/e′ <10, LA volume index normal], grade 2 [moderate diastolic dysfunction or pseudonormal phase: E/A 0.8– 2, DT 160–200 milliseconds, E/e′ 10–14, LA volume index increased], and grade 3 [severe diastolic dysfunction or restrictive filling phase: E/A ≥ 2, DT < 160 milliseconds, E/e′ ≥14, LA volume index increased].

| | Normal | Grade I | Grade II | Grade III |
|---|---|---|---|---|
| LV relaxation | Normal | Impaired | Impaired | Impaired |
| LAP | Normal | Low or normal | Elevated | Elevated |
| Mitral E/A ratio | ≥0.8 | ≤0.8 | >0.8 to <2 | >2 |
| Average E/e′ ratio | <10 | <10 | 10–14 | >14 |
| Peak TR velocity (m/sec) | <2.8 | <2.8 | >2.8 | >2.8 |
| LA volume index | Normal | Normal or increased | Increased | Increased |

**Abbreviations**

| | |
|---|---|
| AC | Anthracyclines |
| CI | Confidence interval |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CRF | Case Report Form |
| CTRCD | Cancer therapy-related cardiac dysfunction |
| CV | CardioVascular |
| DM | Diabetes mellitus |
| DT | Deceleration Time |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| ESC | European Society of Cardiology |
| GCP | Good Clinical Practice |
| GLS | Global Longitudinal Strain |
| GOT | Glutamic-Oxaloacetic Transaminase |
| GPT | Glutamic-Piruvic Transaminase |
| HER-2 | Human Epidermal growth factor Receptor type 2 |
| HF | Heart Failure |
| HFrEF | Heart Failure with reduced Ejection Fraction |
| hs CRP | High Sensivity C-Reactive Protein |
| hs-TnI | High Sensitivity Troponin I |
| HR | Hazard ratio |
| HA | Hypothesis Alternative |
| LVEF | Left Ventricular Ejection Fraction |
| NT-pro-BNP | N-terminal pro b-type natriuretic peptide |
| NYHA | New York Heart Association |
| OMT | Optimal Medical Therapy |
| PI | Principal Investigator |
| QOL | Quality of Life |
| RAAS | Renin Angiotensin-Aldosterone System |
| RCT | Randomized Controlled Trial |
| SGLT-2 | Sodium-Glucose Transporter 2 |
| SGLT2i | Sodium-Glucose Transporter-2 Inhibitors |
| T1DM | Type-1 Diabetes Mellitus |
| TZ | Trastuzumab |
| WHO | World Healt Organization |

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Not applicable.

**Author contributions**

A.G. and V.Q. wrote the main manuscript text. G.R. and L.S. contributed to the conceptualization and overall supervision of the study. A.T., S.S., A.Tu., and M.G. collected and analyzed the data. M.A. and M.D.A. prepared Figures and Tables. C.K. performed the statistical analysis. S.G. and L.D.L. contributed to the clinical interpretation of results. L.P. and A.P. contributed to data curation and literature review. G.U., M.L.C., S.O., and F.G. reviewed and edited the manuscript. G.R. A.G and L.S. were responsible for project administration and final approval of the version to be published. All authors reviewed and approved the final manuscript.

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**Data availability**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
The Ethics Committee of Fondazione IRCCS Policlinico San Matteo has approved the study and its consent to participate [number 0008491/23]. The study will be conducted in accordance with the Declaration of Helsinki. All researchers are trained and certified in Good Clinical Practices. A written informed consent will be taken from all participants.

**Competing interests**
The authors declare no competing interests.

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