MPH Capstone Report

Rationale and Design for the Efficacy and Safety of Empagliflozin on Chemotherapy-induced Heart Failure Prevention Study (EMPA-CHEM HF): randomized, placebo-controlled, Phase 3 trial protocol

By

Vincent Salvador
Master of Public Health Candidate
Johns Hopkins Bloomberg School of Public Health

April 26, 2020

Rationale and Design for the Efficacy and Safety of Empagliflozin on Chemotherapy-induced Heart Failure Prevention Study (EMPA-CHEM HF): randomized, placebo-controlled, Phase 3 trial protocol

Abstract

Mortality from cancer has declined owing to improved cancer screening, diagnosis and treatment. However, a growing number of cancer survivors has developed cardiovascular complications such as heart failure related to chemotherapy. To date, there is no consensus standard preventive regimen against chemotherapy-induced heart failure. There is an unmet need to identify a targeted cardioprotective therapy to minimize the morbidity and mortality related to chemotherapy-induced heart failure. In this research protocol, the primary goal is to investigate the efficacy and safety of empagliflozin compared to placebo in preventing new-onset heart failure among patients diagnosed with cancer and undergoing anthracycline-based chemotherapy. While initially approved for adjunctive treatment of diabetes type 2, previous trials have suggested a substantial benefit of the drug in reducing incidence of heart failure. In this event-driven cardiovascular outcome study, a randomized, double-blind, placebo-controlled design will assess empagliflozin in terms of its efficacy and safety which will be monitored for 36 months. The primary outcome is a composite of cardiovascular death or heart failure events. The key secondary outcome is a composite of major adverse cardiovascular events (MACE) defined as cardiovascular death, myocardial infarction or ischemic stroke. To confirm the superiority of empagliflozin over the placebo, a reduction in hazard risk of composite of cardiovascular death OR heart failure event has to be statistically significant. All primary, secondary and safety outcomes will be adjudicated by the clinical events committee who will be masked of the treatment assignment. Primary analysis of the data will be performed according to intention-to-treat principle. Time-to-event analyses will be derived with the use of Kaplan-Meier estimates and Cox proportional-hazards model. Considering the potential clinical benefit that could be derived from prevention of heart failure from chemotherapy, identifying a novel preventive strategy could offer better patient outcomes and likely decreased healthcare expenses.

Summary of Fulfillment of MPH Goals through Capstone Project

Completing the course requirements for the MPH program in Hopkins has been fulfilling and life-changing. As I conclude my 2 and ½ year as a part-time, online student while juggling my professional responsibilities as a healthcare provider, this capstone project represents the culmination of my curriculum goals. More importantly, it is the discipline and time commitment of going through the process of drafting a research proposal that bears evidence to meeting both my personal and educational goals.

The design of this research proposal has been built on thorough literature review and critical synthesis of the best available evidence to date regarding the research question at hand. With voluminous literatures published online, having the research skill to filter through the massive amount of information is critical to focusing on the primary goal of the research. Formulating the research question and generating the study hypothesis were inspired by a meticulous scientific approach taught in classes in clinical trials. Being able to apply the principles on systematic design of a clinical trial fulfills my personal goals I set from the start, consistent with my personalized track on clinical trials certificate program while exploring other disciplines of the MPH program. Through completion of the graduate program, it has provided me the technical knowledge and skills in designing a trial, conducting sound statistical analysis, calculating sample size and inculcating a deeper understanding of upholding human rights and dignity. Aside from learning how to undertake a scientifically rigorous research, upholding ethical principles when it comes to conduct of research has been an essential part of the educational training. Finally, learning to refine my writing and oral presentation skills in the process of completing the capstone project has been encouraging.

Now that I have acquired some tools of the trade for pursuing a scientifically rigorous, responsible and ethical research, I intend to apply what I have learned to contribute in a meaningful and impactful way in the years to come. It has just started.

JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH
MPH Capstone Project
Clinical Trial Proposal

Rationale and Design for the Efficacy and Safety of Empagliflozin on Chemotherapy-induced Heart Failure Prevention Study (EMPA-CHEM HF): randomized, placebo-controlled, Phase 3 trial protocol

Investigator: *Vince Salvador*
Faculty Adviser: Di Zhao, PhD
Capstone Adviser: Di Zhao, PhD
Date: February 14, 2020/Revised on April 07, 2020/April 26, 2020

I. Primary research question

Among adult patients diagnosed with cancer undergoing treatment with anthracycline-based chemotherapy, does empagliflozin compared to placebo prevent new onset heart failure over 36 months?

II. Study Rationale/Background

Heart failure among cancer survivors

Advancement in the field of oncologic therapeutics has seen cancer mortality rate declining due to improved cancer screening, diagnosis and more effective chemotherapy options (American Society of Clinical Oncology, 2015). With the improvement in cancer survival, there has been mounting recognition of cardiovascular complications such as cardiotoxicity. Left ventricular dysfunction and heart failure are potentially serious side effects of chemotherapy (Zamorano et al., 2016). If not treated early and appropriately, heart failure could progress leading to substantial morbidity and mortality (van der Meer et al., 2019).

According to the U.S. National Cancer Institute, the number of cancer survivors in the United States is expected reach 18 million by 2022 and more than 20 million by 2026 (Miller et al., 2016; Siegel et al., 2012). It has been observed that cancer survivors are at higher risk of dying from cardiovascular diseases compared to the general US population based on a national cancer registry with 40 years of data. Among the cardiovascular diseases, 76% of the deaths are related to heart disease (Sturgeon et al., 2019). While the exact incidence of advanced heart failure among cancer survivors is not known, heart failure registries had provided some insights. The younger age group (44-53 years) and women (62%-72%) have been predominantly afflicted with advanced heart failure related to chemotherapy (Bianco et al., 2017).

Chemotherapy-induced cardiotoxicity

Anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin and idarubicin) are one of the most widely used cytotoxic drugs in cancer treatment. While they have been utilized extensively in the treatment of breast cancer, leukemia, lymphoma and soft tissue sarcoma, their use has been limited by potential myocardial damage which could lead to heart failure. They have been known to cause dose-dependent cardiomyocyte injury and death contributing to eventual development of left ventricular dysfunction and heart failure (Henriksen, 2018). In one study involving 630 patients with lung and breast cancer, the incidence of clinical heart failure following doxorubicin treatment could reach as high as 48% with very high cumulative dose of the chemotherapy (Swain et al., 2003). In addition, increased susceptibility to cardiotoxicity from anthracycline has been seen in female sex, African-American ancestry, age >65 years or < 18 years, renal failure, concomitant exposure of the heart to radiation therapy and predisposing cardiac diseases (Henriksen, 2018).

By definition, cardiotoxicity related to chemotherapy is characterized by a reduction in left ventricular ejection fraction (LVEF) of more than 10% from baseline and less than 50% (Cardinale et al., 2015). Meanwhile, recovery from cardiotoxicity could be categorized as partial (LVEF increase > 5 absolute points and >50%) or full (LVEF increase to the baseline value) (Cardinale Daniela et al., 2015).

The development of cardiotoxicity has traditionally been classified into early and late onset following completion of the anthracycline regimen. However, it has been argued that subclinical cardiac damage forms a continuum in the stage of evolution of chemotherapy-induced cardiotoxicity. After completion of the chemotherapy, an early onset progressive deterioration of LVEF, which could be asymptomatic, may continue for months or years before becoming an overt heart failure. A previous prospective study demonstrated that the median time from the completion of chemotherapy and onset of cardiotoxicity was 3.5 months with majority (98%) of the cases occurring within the first year of follow up (Cardinale et al, 2015).

It was previously thought that anthracycline-induced cardiotoxicity is related to generation of reactive oxygen species (Sawyer, 2013). However a recent study by Zhang et al has supported an alternative model for mechanism of action of anthracycline in causing cardiotoxicity which is primarily attributed to inhibition of topoisomerase 2beta which causes double-stranded DNA breaks which lead to activation of cell death pathways, activation of reactive oxygen species and inhibition of mitochondrial biogenesis (Henriksen, 2018; Zhang et al., 2012).

Preventive strategies for anthracycline-induced cardiotoxicity

For patients at high-risk for developing cardiotoxicity from anthracycline-based chemotherapy, preventive strategies have been recommended such as using dexrazoxane, liposomal doxorubicin, or continuous infusion instead of bolus dosing of the high-dose

anthracyclines (Payne & Nohria, 2017). Due to cost, liposomal doxorubicin is not popularly used and is approved only by the FDA in ovarian cancer, acquired immune deficiency syndrome-related Kaposi sarcoma and multiple myeloma after a failed attempt with the standard treatment (Vejpongsa & Yeh, 2014). To date, dexrazoxane is the only FDA-approved cardioprotective agent for anthracycline-induced cardiotoxicity. However, it has not gained much popularity in clinical use due to safety concerns (Timm & Tyler, 2020).

Cochrane meta-analysis on cardioprotective interventions for cancer patients receiving anthracyclines showed a statistically significant reduction in the occurrence of heart failure with the use of iron chelator dexrazoxane (RR: 0.29, 95% CI 0.20 – 0.41) without evidence of interfering with anti-tumor effect of the chemotherapy and no marked difference in the occurrence of secondary malignancies compared to the control group (Dalen et al., 2011). A more recent network meta-analysis suggested the potential role of dexrazoxane in reducing cardiotoxicity (median pooled OR: 0.26, 95% 0.11-0.74) relative to the control but the quality of supporting data was assessed to be moderate as the patient population had more advanced cancer which was treated more than 20 years ago (Abdel-Qadir et al., 2017). Another meta-analysis evaluating the efficacy of dexrazoxane suggested significant lower risk of developing heart failure compared to control (RR: 0.19, 95% CI 0.09 to 0.40; $p<0.001$) without affecting the cancer outcomes (Macedo et al., 2019). Nonetheless, the studies included in the review were deemed to have low quality and with concerns for multiple sources of bias to allow definitive recommendation for widespread clinical use of the drug as a primary prevention for chemotherapy-induced cardiotoxicity (Macedo et al., 2019). Furthermore, the RCTs included in the meta-analysis were limited to subset of patients who had advanced stage or metastatic disease which necessitated high dose of anthracycline therapy (e.g. doxorubicin >/= 250 mg/m^2) (Armenian et al., 2016).

Uncertainties in prevention of chemotherapy-induced cardiotoxicity

The utility of cardioprotective agents is still fraught with uncertainties. For instance, the American College of Cardiology supports the use of dexrazoxane in high-risk patients to reduce the severity of anthracycline-induced cardiotoxicity (Yancy Clyde W. et al., 2013). Meanwhile, the American Society of Clinical Oncology does recommend the use of dexrazoxane only in patients who plan to receive high-dose anthracycline-based chemotherapy (e.g. doxorubicin >/= 250 mg/m^2, epirubicin >/=600 mg/m^2 (Armenian et al., 2016). Furthermore, there have been evidence concerning bone marrow suppression in all blood components among recipients of dexrazoxane – a finding which has been reported in two meta-analyses and retrospective cohort study (Abdel-Qadir et al., 2017; Dalen et al., 2011; Spalato Ceruso et al., 2019). It must also be noted that dexrazoxane has no effect on survival outcomes (Spalato Ceruso et al., 2019). Both the US FDA and European Medicinal Agency restrict the use of dexrazoxane for metastatic disease requiring high-dose anthracyclines (e.g. >300 mg/m2 of doxorubicin) only (Abdel-Qadir et al., 2017).

Other neurohormonal antagonists routinely used for the treatment of existing heart failure such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers,

mineralocorticoid antagonist and beta-blockers had been explored as treatment options for primary prevention of heart failure. The prospect of utilizing pharmacologic agents that target the preload and afterload components in the pathogenesis of heart failure has led to consideration of neurohormonal blocking agents for primary prevention against chemotherapy-induced cardiotoxicity. However, the available evidence is not yet sufficiently robust to warrant routine application in patients receiving anthracycline-based chemotherapy (Payne & Nohria, 2017). Beta-blocker has been suggested to have potential protective effect for anthracycline-induced cardiotoxicity but the evidence from the largest dedicated trial to date (N=200 patients) has been limited by small sample size, short follow-up period and the use of surrogate outcomes such as decline in LVEF, diastolic dysfunction, troponin and natriuretic peptide level elevation (Avila et al., 2018).

To date, there is no consensus standard regimen given to patients undergoing anthracycline-based chemotherapy to potentially prevent cardiotoxic effects. Therapeutic options for patients developing heart failure are limited to standard heart failure medications which have not been shown to prevent new onset of clinical heart failure. Considering the increasing number of cancer survivors treated with chemotherapy, there is an unmet need to identify targeted cardioprotective therapy to minimize the risk of developing heart failure and its complications.

Potential role of SGLT2 inhibitors for cardioprotection

Three major cardiovascular outcome trials in patients with type 2 diabetes had shown the robust and consistent clinical benefit of SGLT2 inhibitors in preventing the occurrence of heart failure events in patients who did not have prior diagnosis of heart failure (Zelniker et al., 2019). In fact, the rates of heart failure at baseline reported in the three trials ranged from 10%-14% only which implied that the reduction of heart failure events were suggestive of primary prevention rather than secondary (Vaduganathan & Januzzi, 2019). In a meta-analysis of trials involving the 3 different SGLT2 inhibitors (i.e. empagliflozin, canagliflozin and dapagliflozin), it has been demonstrated that the drug reduced the relative risk for heart failure hospitalization by 31% (0.69 [0.61-0.79], $p<0.0001$), irrespective of the presence of atherosclerotic cardiovascular disease or a history of heart failure (Zelniker et al., 2019). This has been unprecedented and unexpected magnitude of benefit from the different classes of antihyperglycemic drugs which has been in the market for decades (Packer, 2019). Among the glucose-lowering drugs for diabetes, only SGLT2 inhibitors have been reported to have substantive benefit on reducing cardiovascular events through reducing the risk of developing heart failure (Packer et al., 2017).

The remarkable results from the SGLT2 inhibitor trials have brought into the spotlight the potential role of this class of anti-glycemic drug as an adjunctive therapy for the management of heart failure irrespective of the baseline history of heart failure and diabetes type 2 status (Vaduganathan & Januzzi, 2019). While the exact biologic mechanism of the drug needs to be elucidated in both mechanistic and large outcome trials, there is a potential utility of the drug as a preventive regimen for patients undergoing cardiotoxic chemotherapy.

The huge benefit in the reduction of heart failure hospitalization exhibited in the landmark trials has been suspected to be related to mechanisms distinct from improved glycemic control which has been modest as evidence by 0.5%-1% reduction in mean glycated hemoglobin (Lan et al., 2019). Potential mechanisms of the benefits of the drug class have been conceptualized based on post-hoc analysis of trials and animal models. It has been proposed that the protective benefits of the SGLT2 inhibitors in heart failure could be mediated by promoting viability of cardiomyocytes, improvement in ventricular loading conditions by reducing preload and afterload, inhibition of the Na+/H+ exchange, regulating adipokines and cytokine production, and reduction of necrosis and cardiac fibrosis while attenuating pathways that contribute to cardiomyocyte apoptosis (Packer, 2019; Tentolouris et al., 2019).

Far from their effect on glycemic control and osmotic diuresis, SGLT2 inhibitors appear to have beneficial effect in heart failure though its inhibitory effect in the proximal renal tubule through sodium-hydrogen exchanger which is upregulated in experimental models of heart failure. While there are no detectable expression of SGLT2 in the cardiomyocytes, it has been postulated that SGLT2 inhibitors downregulate the activity of sodium-hydrogen exchanger-1 (NHE-1) in the cardiomyocytes. Interference with the NHE-1 activity prevents the increase in intracellular calcium which has been linked to loss of cardiomyocytes (Packer, 2019). Furthermore, inhibition of the NHE attenuates the development of cardiac hypertrophy, fibrosis, remodeling, systolic dysfunction and heart failure based on experimental models (Packer et al., 2017).

Preclinical studies have also indicated that the mechanism of cardioprotection could be mediated by cellular master regular through adenosine monophosphate-activated protein kinase (AMPK) activation. As a therapeutic target in heart failure, AMPK activation leads to increased mitochondrial biogenesis, promoting autophagy and decreased fibrosis. In particular, it has also been suggested that SGLT2 inhibitors can activate AMPK in cardiac fibroblasts and adipocytes (Timm & Tyler, 2020).

Potential value of empagliflozin in prevention of chemotherapy-induced cardiotoxicity

Among the SGLT2 drugs available in the market, empagliflozin has been investigated in preclinical studies for its potential to prevent doxorubicin-induced cardiotoxicity. Empagliflozin is a selective sodium-glucose cotransporter 2 (SGLT2) inhibitor which has been approved for use in the treatment of type 2 diabetes. The expert consensus recommended it for consideration as second-line therapy for people with type 2 diabetes and cardiovascular disease to prevent the onset of heart failure and cardiovascular mortality (Ponikowski et al., 2016). It's glucose-lowering action is mediated by reducing renal glucose reabsorption in the proximal renal tubules and thereby increasing urinary glucose excretion (Gallo et al., 2015). Among the commercially available drugs from its class, empagliflozin has the highest selectivity for SGLT2 than SGLT1 (Tentolouris et al., 2019). Just like other SLGT2 inhibitors, it has also been shown to cause osmotic diuresis, reduce weight and blood pressure, and decrease the risk of heart failure events (Fitchett et al.,

2016). The most notable side effects from empagliflozin were urinary tract infection and genital yeast infection (Boehringer Ingelheim, 2014; Zinman et al., 2015).

In animal study involving mice, it was demonstrated that empagliflozin has both anti-inflammatory and cardioprotective effects in doxorubicin-induced cardiotoxicity through inhibition of lipid peroxidation, reduction of leukotriene-B4, attenuation of NF-kB activation, and inhibition of interleukin 1beta, 8 and 6 production (Maurea et al., 2019). It has also been reported that empagliflozin increased serum beta hydroxybutyrate levels which improved cell viability and reduced reactive oxygen species (ROS) generation (Oh et al., 2019). In vitro study involving mice model have demonstrated anti-inflammatory activity of empagliflozin by reducing both leukotriene B4 and NF-kB expression in Doxorubicin exposed cells (Quagliariello et al., 2019). Furthermore, there was less degree of myocardial fibrosis and reduction of fibrillar bands on histologic evaluation of the mice myocardium exposed to doxorubicin but treated with empagliflozin (Soloveva et al., 2017).

Dedicated trial to demonstrate the efficacy and safety of empagliflozin in preventing anthracycline-induced cardiotoxicity is of paramount importance to fill the gap in identifying a therapeutic target in preventing heart failure among patients undergoing cytotoxic chemotherapy. As of the present, there are no published trials exploring the effect of empagliflozin as a therapeutic strategy in preventing heart failure among patients with cancer treated with anthracycline-based chemotherapy.

III. Primary hypothesis

The trial is designed to evaluate the efficacy and safety of empagliflozin for primary prevention of anthracycline-induced cardiotoxicity. The primary hypothesis is superiority of empagliflozin relative to placebo for the primary outcome in terms of reduction in hazard risk of composite of cardiovascular death OR heart failure events in patients undergoing anthracycline-based chemotherapy. The hazard ratio will be estimated using Cox proportional hazards regression model.

The assumption for this superiority trial posits the null hypothesis being that there is no difference in the primary outcome between the two treatment groups. To conclude superiority, the null hypothesis needs to be rejected. The superiority of the primary outcome is determined if the upper boundary of the 95% confidence interval of the hazard ratio for the primary outcome is less than 1.0.

IV. Secondary hypothesis

The secondary hypothesis to be tested is the superiority for the secondary outcome which includes the following: (1) composite of major adverse cardiovascular events (MACE) - defined as cardiovascular death, myocardial infarction or ischemic stroke; (2) change in

the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months; and (3) death from any cause.

V. Method

A. Trial design

Randomized, parallel, double-blind, placebo-controlled, multicenter, Phase III trial to evaluate the efficacy and safety of once-daily empagliflozin (10 mg) compared to placebo in reducing primary and secondary composite outcome measures.

B. Treatment group

Patients randomized in the treatment group will be given daily dose of empagliflozin 10 mg by mouth starting on the 1st day of chemotherapy until the last day of the entire chemotherapy regimen. There is a valid clinical equipoise on the potential role of empagliflozin in chemotherapy-induced cardiotoxicity. Using any SGLT2 inhibitors as a primary preventive strategy has not been studied among patients who are high-risk of developing cardiac complications from chemotherapy.

In cases of medical necessity, background therapy for existing chronic medical problems and/or cardiovascular risk factors will be continued to provide the best available standard of care according to the local guidelines.

C. Control group

The control group will be provided a daily dose of placebo pill starting on the 1st day of chemotherapy until the final day of chemotherapy regimen. At the present, the use of cardioprotective agent such as dexrazoxane is not a standard routine practice for all patients undergoing anthracycline-based chemotherapy. Furthermore, the use of dexrazoxane is only recommended in advanced cases requiring high-dose anthracycline regimen.

D. Randomization plan

Informed consent will be obtained from the patients prior to screening. After completing the screening, eligible patients will be randomly assigned to either empagliflozin (at a dose of 10 mg) or a matching placebo based on a fixed-randomization schedule. Both regimens will be continued until the completion of chemotherapy. Randomization will be done centrally using a computer-generated randomization scheme with variable permuted blocks of fixed 1:1 assignment ratio of the two regimens. In view of potential confounding effect from relevant variables, the randomization will be stratified on the basis of: (1) trial sites and (2) presence of prior atherosclerotic cardiovascular disease (ASCVD) by clinical history. By definition, ASCVD includes any of these prior clinical outcomes: acute coronary syndromes, stable or unstable angina, arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin (Arnett et al., 2019).

The data on randomization sequence will be concealed and maintained by an independent central coordinating study site.

E. Masking

Patients, trial investigators, outcome assessors and data analysts will be masked to the treatment assignment during the conduct of the trial using a placebo pill that appears similar to the experimental drug (empagliflozin). Unmasking of treatment will only be done with approval of the principal investigator at the completion of the entire trial or in the event of serious adverse events which would warrant proper identification of the drug given to the patient to guide appropriate treatment.

F. Major eligibility criteria: inclusion and exclusion criteria

Patients eligible for enrollment must be: at least 18 years of age at the time of screening, diagnosed with cancer which will be treated with anthracycline-based chemotherapy.

Exclusion criteria include prior history of symptomatic heart failure (either HFrEF or HFpEF), presence of cardiomyopathy, systolic dysfunction defined as baseline LVEF<50%, diabetes mellitus type 1, impaired renal function defined as eGFR<30 cc/min by Cockroft-Gault equation, prior chemotherapy or radiotherapy involving the chest, active breastfeeding, pregnancy or planning to becoming pregnant while on the trial, and active participation in another trial.

VI. Outcomes

A. Primary outcome

The primary outcome is a composite of cardiovascular death or heart failure event expressed as time-to-event, aggregated as hazard ratio, over 36-month period with onsite follow-up at 6-month interval. Heart failure event includes hospitalization, urgent clinic visit or emergency room visit due to heart failure exacerbation (Hicks et al., 2018).

B. Secondary outcomes

The key secondary outcome is a composite of major adverse cardiovascular events (MACE) defined as cardiovascular death, myocardial infarction or ischemic stroke (Hicks et al., 2018). Additional secondary outcomes include change in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months and death from any cause. KCCQ total symptom score ranges from 0-100 with higher scores indicating fewer heart failure symptoms and >/= 5-point interval change in score is considered clinically meaningful (Green et al., 2000).

To guide the systematic data collection and increase the reliability of results, a uniform definition of cardiovascular outcomes will be adopted based on Standardized Data Collection for Cardiovascular Outcomes Trials (Hicks et al., 2018).

C. Safety analyses

A prespecified safety outcome analysis will be reported as incidence rates over the same time period for each treatment groups. This will include serious adverse events, adverse events related to discontinuation of the treatment, and adverse events of interests such as urinary and genital infections, volume depletion, acute renal failure, hypoglycemia, ketoacidosis, amputations and thromboembolic events.

All primary, secondary and safety outcomes will be adjudicated and confirmed by the members of the clinical events committee who will be masked of the treatment assignment. Figure 1 provides the schematic outline of the trial design.

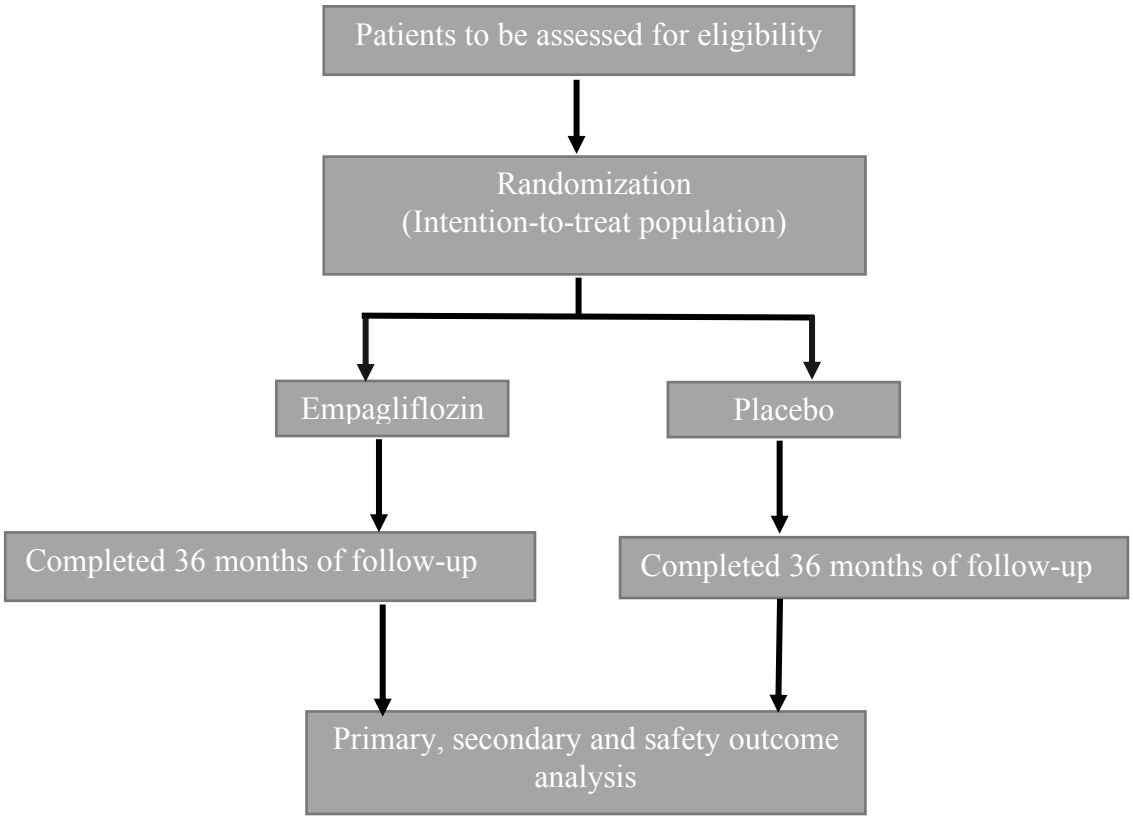

Figure 1. Trial Schema of EMPA-CHEM HF

VII. Data collection (with data collection schedule table)

Patients will be evaluated in the clinic at predefined time points after randomization to evaluate clinical status, adverse events and perform biomarker testing (troponin, BNP) and imaging study (2-D echo). The full schedule of assessment is provided in the table 1 below.

Data entry will be distributed in all trial sites. Data encoding will be completed through internet-based electronic data capture. Access to the data management system will be provided only to authorized study personnel with unique access codes. There will be built-in data entry validation in the electronic database. The central coordinating site will have full access to the data from all sites.

A face-to-face clinic follow up visit will be scheduled every 6 months starting from the date of randomization with telephone contact follow up between the clinic visits. Patients will be assessed of the prespecified primary and secondary outcomes, adverse effects and adherence to regimen during the clinic visits. Phone call follow-ups will be scheduled in between the clinic visits to assess patients' medication compliance and potential side effects.

Patients who prematurely drop out will still be followed to ascertain vital cardiovascular outcomes, if possible, until the completion of the entire follow up duration for 36 months. Sufficient follow-up visits will facilitate assessment of clinical and safety outcome measures.

Table 1. Data collection schedule

	S	E	Follow up visits (months) from day of randomization												
Timepoint	-1	0	1	3	6	9	12	15	18	21	24	27	30	33	36
Type of Visit															
Screening visit	✓														
Enrolment visit		✓													
Interval follow up clinic visit			✓		✓		✓		✓		✓		✓		✓
Phone call follow up				✓		✓		✓		✓		✓		✓	
Procedures															
Obtaining consent	✓														
Eligibility screen	✓														
Randomization		✓													
2-D echo assessment	✓				✓		✓		✓		✓		✓		✓
Lab tests	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Baseline demographic gathering	✓														

Medical history	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
KCCQ assessment	✓				✓										
Physical exam	✓	✓	✓		✓		✓		✓		✓		✓		✓
Review of compliance			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Review of adverse reactions			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispensing of study drug		✓		✓		✓		✓		✓		✓		✓	

*S-screening for eligibility criteria; E-enrolment in the trial

VIII. Statistical Analysis

A. Sample size determination and assumptions

Using the log-rank test (Freedman method in STATA/IC version 15.1), it is estimated that enrollment of approximately **314 patients (N=157 per treatment arm)** will be required to accrue 314 primary outcome events in order to have 90% power to detect an observed hazard ratio of 0.69 for the comparison between empagliflozin and placebo, using a two-sided significance level of 0.05 in a superiority trial. Accounting for possible 25% dropout rate, the adjusted total sample size will be **418 (N=209 per treatment arm)**.

B. Statistical analysis plan of primary and secondary outcomes

Primary analysis of the data from all the patients who underwent randomization will be performed according to the intention-to-treat principle. Baseline data will be summarized as means and standard deviations, medians and interquartile ranges or percentages. Time-to-event analyses will be derived with the use of Kaplan-Meier estimates and Cox proportional-hazards model, stratified according to trial sites and presence of established ASCVD. The cumulative incidence of the composite of CV death and heart failure event, composite of MACE, and deaths from any cause will be estimated by Kaplan-Meier method. Hazard ratios, 95% confidence intervals and P-values will be calculated from the model.

Data derived from KCCQ will be analyzed as a composite, rank-based outcome comparing change in score from baseline to 6 months and vital status at 6 months using rank analysis of covariance method (Quade, 1967). KCCQ is a validated heart failure-specific health status measure which is conveniently quantifiable as total score ranging from 0 to 100 with higher scores correlating with fewer symptoms and less physical limitations due to heart failure (Green et al., 2000). The treatment effect in terms of total symptom score on KCCQ will be expressed as win ratio where a value greater than 1 indicates superiority (Wang & Pocock, 2016).

Patients who will not experience the outcome event will be censored on the last day they are known to be free of the outcome of interest. For missing data, analysis will be based on

likelihood method with the assumption that data were missing at random. Sensitivity analysis of the primary and secondary efficacy and safety outcomes according to as-treated approach will be performed to identify potential differential effect on the estimates derived from primary analysis. Safety analyses will be performed on patients who underwent randomization and have received at least a dose of either empagliflozin or placebo. Incidence of adverse events in both treatment arms will be compared using Fisher's exact test. All analyses will be performed using Stata software version 15.1.

C. Ancillary analyses (subgroup analysis)

Consistency of treatment effect for the primary composite outcome will be evaluated using Cox regression analysis across prespecified subgroups which include (1) age </= 65 or > 65; (2) male or female; (3) race as identified by patient – White, Black, Asian, Hispanic, Others; (4) presence of ASCVD – yes/no; (5) presence of diabetes mellitus at baseline-yes/no; (6) Baseline eGFR<60 or >/=60; (7) >/= 10% reduction in LVEF at 6, 12, 18, 24, 36 months; (8) NT pro-BNP level </= median or > median at 6, 12, 18, 24, 36 months; (9) troponin I > 0.04 ng/mL or </= 0.04 ng/mL at 6, 12, 18, 24, 36 months; (10) presence of diastolic dysfunction at 6, 12, 18, 24, 36 months; (11) use of statins at baseline; (12) use of antihypertensive therapy at baseline; (13) BMI <30 or >/=30; (14) BP control >/=140/90 or <140/90.

IX. Safety monitoring and assessment

The trial will be overseen by an independent Data and Safety Monitoring Board (DSMB) which will have an official committee charter drafted prior to reviewing the trial results. Members of the DSMB will be composed of voting and non-voting members. As a rule, voting members should not be directly involved in the trial implementation and should not have affiliations with the sponsor. Safety outcome data will be reviewed by the DSMB every 90 days or at the discretion of the committee members. Only the members of the DSMB will have access to the interim results and make the recommendation on the progress of the trial. Furthermore, DSMB will have direct access to the source data and other trial-related documents. The DSMB will not be masked of treatment assignment.

All adverse events, irrespective of the severity, will need to be reported by the primary investigator to the sponsor and local IRB following the reporting requirements of International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice and the local regulatory authorities. In turn, the study sponsor is required to report adverse events to the DSMB.

In the event of lost to follow up during the trial, patients will still be followed to ascertain primary, secondary and safety outcomes. Attempts will be made to collect vital information from any patient who will drop out of the study prematurely.

X. Ethical considerations and Plan for dissemination

The protocol will have to be approved by the Institutional Review Board (IRB) at each participating site prior to enrolling any patients. To participate in the trial, all patients will need to provide a written consent prior to the initial screening when baseline information are obtained and eligibility criteria are checked. All patients will be informed about the research objectives, study protocol and treatment alternatives in obtaining the consent.

All personal health information will be kept confidential and secured in a central computer database. Patients' personal information will remain confidential in any publications generated from the current trial. Only approved study investigators and personnel will be given authenticated access to the data files. Personal health information may be shared with the following relevant authorities for review: sponsor, local IRB, DSMB, FDA and NIH.

Prior to the initiation of the trial, the design and its specification will be published and the trial will be officially registered in ClinicalTrials.gov. The entire study protocol and statistical plan will be made public when results are published in a scientific journal. Patient-level data sets can be shared upon written request and signing an agreement on the proper use of the deidentified data sets. Data can be shared for secondary analysis after completion of the trial provided they are deidentified in compliance with Health Insurance Portability and Accountability Act (HIPAA) guidelines.

Biologic specimens collected during the trial will not be used in any genome-wide association studies and for any commercial purposes. Investigators will not be sharing any genomic data for future studies without the approval of the patients in the trial.

XI. Randomization Form

Purpose: To verify eligibility for randomization and document the masked treatment assignment

When: To be completed during the enrollment visit after completing eligibility evaluation and baseline laboratory diagnostics during the screening visit

Instructions: If a participant meets eligibility criteria on initial assessment, fill out this form and key into the database system prior to obtaining treatment assignment. Items marked with STOP mean patient is ineligible.

A. Clinic site, participant and visit ID

1. Clinic site ID: ___ ___ ___ ___ ___
2. Patient ID:___ ___ ___ ___ ___ ___
3. Visit ID code: ___ ___ ___ ___ ___
4. Date of Randomization: ___ ___-___ ___-___ ___ ___ ___
   Month Day Year
5. Form version date: **03 – 11 – 2020**
   Month Day Year

B. Inclusion criteria for randomization

6. At least 18 years of age or older at the time of screening:

Yes	No
(1)	(2)

7. Has been diagnosed with cancer which will be treated with anthracycline-based chemotherapy:

Yes	No
(1)	(2)

C. Exclusion criteria for randomization

8. Prior history of symptomatic heart failure (either heart failure with reduced ejection fraction or heart failure with preserved ejection fraction)

Yes (1) No (2)

9. Presence or prior history of cardiomyopathy

Yes (1) No (2)

10. Presence of baseline LVEF < 50%

Yes (1) No (2)

11. Diagnosis of diabetes mellitus type 1

Yes (1) No (2)

12. Had prior systemic chemotherapy or localized radiotherapy on the chest

Yes (1) No (2)

13. Currently breastfeeding, pregnant or planning to become pregnant while on the trial

Yes	No
(1)	(2)

14. Actively participating in another trial

Yes	No
(1)	(2)

15. Renal function:

    a. Serum creatinine: __ __. __ __ mg/dL

    b. Estimated creatinine clearance (defined by Cockroft-Gault equation): __ __.__ __ mL/min

    c. Creatinine clearance less than eGFR < 30 mL/min

Yes	No
(1)	(2)

D. Final check

16. Patient meets all eligibility criteria for randomization

Yes	No
(1)	(2)

E. Administrative information

17. Date form reviewed:___ ___-___ ___-___ ___ ___ ___
    Month Day Year

18. Site coordinator PIN:___ ___ ___ ___ ___

19. Site coordinator signature:_____

20. Study physician PIN:___ ___ ___ ___ ___

21. Study physician signature:_____

22. Dare study physician signed:___ ___-___ ___-___ ___ ___ ___
    Month Day Year

After entering the information from this randomization form in the computer system, go the Data Systems Menu and select Treatment Assignment. Record the treatment group alphanumeric code provided in the computer in the space indicated below.

F. Randomization data

23. Treatment assignment code:___ ___ ___ ___ ___ ___

XII. Informed Consent Template document

Protocol Title: *Rationale and Design for the Efficacy and Safety of Empagliflozin on Chemotherapy-induced Heart Failure Prevention Study (EMPA-CHEM HF): randomized, placebo-controlled, Phase 3 trial protocol*

Application No.: XXX-XXX-XXX

Sponsor/Funder: Pending

Principal Investigator: Vince Salvador/Vincent.Salvador@jhu.edu

Summary

- This study will look into how a drug can prevent the development of failing heart which is caused by a particular standard chemotherapy regimen for cancer.
- Participation in this study is voluntary. You may stop at any time. If you decide to join this study, your personal information and specimens will be collected.
- This study will be carried out for 36 months. Interval clinic visits are scheduled every 6 months to keep track of your health condition.
- There is no guarantee that you will benefit by joining this study. There are also possible side effects that you need to be aware of.
- This study has been approved by experts who are responsible for ensuring the safety of participants in the study.

What is this study about?

- **You are eligible to take part in this research study.** This document explains the details about joining the study. It is highly recommended that you discuss any questions you have about this study with our research staff, your doctor, and your family. Please read this document carefully before making your decision if you would like to join the study.

- **You are joining the study on voluntary basis.** The decision is on you whether you like to participate. Your decision to join or not will have no effect on the provision of medical services you are receiving from our clinic. You will still be provided the standard care and treatment in our clinic if you decide not to join the study.

- **You can always decide to stop participating in the study at any time even if you agree to participate at the start.** Should you decide to stop participating in the study after receiving a single dose of the drug, our research staff will still be following up with you to check on your health status.

- **Updating your primary doctor about you joining the study is highly advisable.** It is important that your primary doctor knows that you are participating in the study to make sure that your health condition will be monitored closely for any adverse effects.

- **This study is a clinical trial.** The purpose of conducting this study is to gather information on the effectiveness and safety of a drug on decreasing the risk of developing heart failure and dying from it. The drug we are using in this study is called ***empagliflozin***. This drug has been tested before in people with diabetes type 2. Approximately 400 patients will participate in this study. Some of the patients will not be given the actual drug. Instead, they will be given a "dummy pill" which looks like the real drug but is not. The "dummy pill" has no effect on you because it has no active drug in it. If you decide to participate in the study, you will be informed about the final results at the completion of this study.

- **There will be scheduled clinic follow-up visits every 6 months for 36 months if you decide to participate in this study.** This follow-up visits is important to monitor your health condition while in the study.

Why is this study being done?

- **This study will evaluate if empagliflozin can help prevent death from heart disease or hospitalization due to failing heart.** Previous studies have shown that the drug can decrease the risk of death from heart disease and hospitalization related to failing heart among patients with and without diabetes type 2. However, it is not clear if the drug could also be used among patients who have cancer that requires chemotherapy that might affect the heart in a negative way. We do not know if the drug can prevent new occurrence of failing heart and prevent death if used among patients with cancer requiring chemotherapy that involves anthracyclines.

- **There have been no studies done that looked into using the drug to prevent the occurrence of heart failure as a complication of chemotherapy treatment among patients with cancer.** This study will attempt to answer the question on the potential benefit of the drug in the prevention of the heart condition.

- **We anticipate approximately 400 people to participate in this study throughout the country.** This will be conducted in multiple clinics and hospitals throughout the country. However, it is possible that we might not reach the target total number of patients to be enrolled within the given time due to lack of interest from patients or the study gets terminated by the investigators.

What to expect if you join the study?

- **The study will last for 36 months.** You could be participating in the study for a shorter time if it gets cancelled by the investigator. During the actual study, it is important that you attend follow-up visits every 6 months until the study is completed. In total, you will be requested to come to the clinic 7 times. During the follow-up visits, you will be assessed by a doctor. Blood tests and imaging of your heart will be completed as well.

- **There will be follow-up telephone calls in between the clinic visits**. These follow-up phone calls will be made by our research staff to check your health condition and verify if you're taking your medication properly. We will be doing these phone calls until you complete or leave the study.

- **If you decide to participate in this study, you will be randomly assigned to either the active drug – empagliflozin or the dummy medication on the first day of your chemotherapy schedule.** The group you will be assigned to will be chosen by chance. We will do it by randomization which is like tossing a coin. You will have equal chance of getting the active drug or the dummy medication. Neither you nor your doctor will know the identity of the drug you are assigned to until the completion of the study. This is our way of making sure that we will not be influenced by our expectation of the medication you are taking. Whichever drug you end up assigned to, you can still continue taking the rest of your routine home medications.

- **Your doctor will provide you a 3-month supply of the medication for free.** The medications will be paid by the study sponsor and funder of the study.

- **As part of participating in the study, your personal health information will be collected from the health records.** This will include the electronic medical records and insurance records. All information we collected will remain confidential. The information may be shared to the members of the DSMB for safety review.

What are the risks and discomfort in joining the study?

- **There is no guarantee that your heart will be protected from the effect of chemotherapy by taking the active drug.** It is possible that your heart condition can get worse through time after completing the chemotherapy.

- **You may experience some side effects from the medication based on what we have seen in previous studies.** Some people might experience the side effects and some people would not have any side effects at all. It is also possible you might develop side effects that we have not seen before. While you are in this study, we will monitor your condition closely. If you develop side effects, we might use other medications to treat them. If needed, we might also stop your study medication completely, if necessary. You will be made aware if we decide to stop your study drug.

- **These are the known potential side effects one might experience while taking the drug:**

    1. Yeast infection in the genitalia and urinary tract which could present as painful urination, rashes, redness, warmth and stinging sensation on the genitalia or groin (9%)
    2. Dehydration which could happen if your body does not have enough fluid because of too much fluid lost from urination (3%)
    3. Frequent urination (3%)
    4. Bone fracture (2%)
    5. Feeling nauseated (2%)
    6. Excessive thirst (2%)
    7. Low blood sugar (1%)
    8. Fainting spells (<1%)
    9. Generalized body weakness (1%)
    10. Kidney damage with resulting worsening kidney function (<1%)
    11. Infection in the urine (1%)
    12. Blood pressure dropping upon standing (1%)
    13. Allergic reaction like skin rashes, swelling of face, tongue and throat (1%)
    14. Stroke and thromboembolic events such as blood clots in the legs or lungs (0.6%)
    15. Diabetic ketoacidosis manifesting with increased urination, increased thirst, abdominal pain, nausea/vomiting and confusion (0.1%)
    16. Lower leg or foot amputation (0.5%)

- **It is possible that some patients who takes the "dummy pill" might also experience similar side effects but at lesser degree.** We have seen in previous studies that the side effects of the active drug are almost similar to the dummy pills.

- **You can stop the medication at any time during the study.** If you finally decide to stop taking your medication, we will be reaching out to you by phone to check your health condition and assess potential side effects. If needed, we can also schedule for a follow-up clinic visit for you to be seen by a doctor.

- **If you develop any side effects from the drug, it is important to notify us immediately by phone or email.** Whether it is a minor or a major adverse reaction/s that require treatment in the clinic or hospital, you are encouraged to inform the study team. You can reach the study team 24/7 by phone at <XXX> or email at <XXX>.

What are other risks in this study?

- **You might feel inconvenienced by the frequency of follow-up calls and clinic visits**. During these follow-up sessions, you will be asked certain questions to check how you are doing. In some clinic visits, you will also have to get blood draws and get imaging of your heart. The blood draws will be done by a trained phlebotomist using either of your arms. The imaging of your heart will be done with an ultrasound held on your chest.

- **You might get frustrated with follow-up reminders you will be receiving during the study.** You have the option to request to stop the reminders. These reminders are put in place to ensure that you will be taking the medications as prescribed and will attend the follow-up visits in the clinic.

What are the risks in pregnancy?

- **If you are currently pregnant or planning to conceive while in the study, you are not eligible to participate in the study.** There are side effects that are difficult to predict for pregnant women. It is possible that the drug might affect the baby. Prior to enrollment in the study, you will be asked to get a pregnancy test which will be provided free of charge.

What are the benefits in joining the study?

- **If you happened to be assigned in the group that receives empagliflozin**, you may benefit from reducing the risk of unexpected death from heart disease and/or prevention of hospitalization due to new occurrence of a failing heart. There is no guarantee however that you will get health benefits from being in this study.

- **The results of this study may help guide development of future treatment of heart failure.** This study will help the future generations to understand how to prevent the condition after being exposed to a chemotherapy known to cause heart problems.

What other treatment options you have?

- **Your participation in this study will not affect your options to get medical treatment in the clinic.** If you decide not to join in this study, your doctor can provide you medication appropriate for your health condition. The medication being investigated in the study is meant to be used for prevention of failing heart due to chemotherapy for your cancer.

- **At the present, there is no routine standard medication being given during chemotherapy to prevent heart complications.** Some doctors would offer dexrazoxane if very high doses of the chemotherapy will be given. Others might use standard medications based on guidelines for treatment of existing heart failure. You can consult with your doctor about these treatment options.

- **You can also consider taking part in another research study.** There are other studies that are looking into prevention of heart failure among patients receiving chemotherapy regimen for cancer. You have the option of joining another study.

- **You may also decide not to get any treatment at all.** It is your personal choice if you want to receive the experimental medication during your chemotherapy. Your chemotherapy regimen will still be provided even if you decide not to participate in this study.

What costs are associated with this study?

- **There are no costs for the study medications, blood tests and heart imaging.** The medication, laboratory tests and imaging will be paid by the sponsor/funder. If complications or injuries arise as a result of the medication being used in the study, the sponsor will pay for the medical treatment of the complications or injuries.

Is there a monetary compensation for joining the study?

- **There is no other monetary compensation for being in this study.** You will not be given any other financial incentives in joining the study.

What if you decide to stop participating in the study?

- **You can decide to end your participation in the study any time.** There will be no penalty or loss of benefits to which you are entitled to receive in the clinic. Your treatment in this clinic will not be affected in any way by your decision to stop.

- **It is possible that research staff will recommend ending your participation in the study.** This might happen if you develop serious adverse effects from the drug, you become pregnant while in the study or if the study gets terminated early by the research staff themselves.

How will your personal information be used?

- **By agreeing to join this study, you are giving permission to us to use your personal health information.** We will keep your information confidential. But we cannot guarantee absolute privacy since some information might need to be examined by independent groups to protect your wellbeing such as DSMB, FDA, NIH. Your permission to use and share the protected personal health information has no time limit.

- **Only the relevant medical information will be collected from your electronic medical record.** This will include medical history, blood tests and imaging results. To access the vital information, we will have to get your complete name, home address, date of birth, social security number and health insurance details.

- **Your health information is protected by law.** There are federal and state policies such as HIPAA to protect your privacy. Your personal health information may be given out if mandated by the law.

- **Your personal health information may be shared with the following authorized representatives who will oversee the conduct of the study:** sponsor, local IRB, DSMB, federal agencies such as FDA and NIH.

- **You cannot join the study if you do not want any of your personal health information be used and shared in this study**.

- **You are free to cancel your permission at any time.** If you decide to cancel your permission, your participation in the trial will automatically be terminated. However, you will still be followed closely to assess your health status.

What will happen if you get injured in the study?

- **Your safety is our first priority. We will do our best to prevent injury as a result of your participation in the study.** In the event you develop injuries as a result of the drug used in the study, the study sponsor will pay for all the costs of the medical treatment. Other extra costs not covered will be passed to your health insurance.

- **You are not giving up your rights to seek compensation for injuries if you sign this document.** If you have any concerns or adverse effects to report, you can call us at <phone number> or send an email at <email address>. In case of any emergency you are advised to seek medical assistance immediately and call 911.

How will your specimen and information be used?

- **Your blood samples and imaging records will be used in analyzing the data in this study.** We will not be sharing your blood samples or imaging reports with other researchers. We will also not share your personal information to other parties unless mandated by governing laws and policies. Your blood samples will not be used for genetic studies.

- **There may be new important information that we will learn from the study about your specimen or information.** The researchers may not share these results with you, depending on a lot of factors.

- **The study will not use your specimens to examine your DNA.** This process is called "whole genome sequencing." Your DNA contains important information about your physical traits and health. We will not perform genome sequencing as part of this study.

- **Your specimens will not be used by the research staff for commercial purposes.** There is no plan to design a product or services for profits using your own specimen material. All specimens will be used to obtain prespecified data elements to aid in answering the main questions of the study.

What other things you need to know about the study?

- **This study has been reviewed by Institutional Review Board (IRB)** which is a committee who is responsible for protecting the safety and welfare of patients in the study. If you wish to get in touch with the representative of IRB, you can call <phone number>.

- **This study is being funded by research grant** from <name of sponsor or pharmaceutical company>. The investigators have no conflict of interest to declare.

- **The findings of the study will be shared with you by email.** This will be done after the publication of the results in a peer-reviewed medical journal. All personal identifiable information will remain anonymous. Only the aggregated data will be presented.

- If you have further questions or clarifications about the study, please feel free to contact us at <insert phone number/email address> Mondays through Fridays at 8:00 AM until 4:00 PM (ET).

What does it mean to sign this document?

- In signing this document, it implies that (1) you *understand* the information shared to you in this document; (2) you *accept* the conditions identified in this document; and (3) you *voluntarily agree* to join in this study.

You will be given a copy of this signed and dated form.

Your signature below attests that you have received information about the study, have reviewed the information, had the opportunity to ask questions from the staff and had received answers to those questions to help you decide.

By signing this form, you agree to voluntarily take part in this study. You also allow us to collect your personal health information in the study.

_____	_____	_____	_____
Signature of Patient	**Printed Name**	**Date**	**Time**
_____	_____	_____	_____
Signature of Person obtaining the consent	**Printed Name**	**Date**	**Time**

XIII. References

Abdel-Qadir, H., Ong, G., Fazelzad, R., Amir, E., Lee, D. S., Thavendiranathan, P., & Tomlinson, G. (2017). Interventions for preventing cardiomyopathy due to anthracyclines: A Bayesian network meta-analysis. *Annals of Oncology: Official Journal of the European Society for Medical Oncology*, *28*(3), 628–633. https://doi.org/10.1093/annonc/mdw671

American Society of Clinical Oncology. (2015). The state of cancer care in america, 2015: A report by the american society of clinical oncology. *Journal of Oncology Practice*, *11*(2), 79–113. https://doi.org/10.1200/JOP.2015.003772

Armenian, S. H., Lacchetti, C., Barac, A., Carver, J., Constine, L. S., Denduluri, N., Dent, S., Douglas, P. S., Durand, J.-B., Ewer, M., Fabian, C., Hudson, M., Jessup, M., Jones, L. W., Ky, B., Mayer, E. L., Moslehi, J., Oeffinger, K., Ray, K., … Lenihan, D. (2016). Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology*, *35*(8), 893–911. https://doi.org/10.1200/JCO.2016.70.5400

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., Himmelfarb, C. D., Khera, A., Lloyd-Jones, D., McEvoy, J. W., Michos, E. D., Miedema, M. D., Muñoz, D., Smith, S. C., Virani, S. S., Williams, K. A., Yeboah, J., & Ziaeian, B. (2019). 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *74*(10), 1376–1414. https://doi.org/10.1016/j.jacc.2019.03.009

Avila, M. S., Ayub-Ferreira, S. M., de Barros Wanderley, M. R., das Dores Cruz, F., Gonçalves Brandão, S. M., Rigaud, V. O. C., Higuchi-Dos-Santos, M. H., Hajjar, L. A., Kalil Filho, R., Hoff, P. M., Sahade, M., Ferrari, M. S. M., de Paula Costa, R. L., Mano, M. S., Bittencourt Viana Cruz, C. B., Abduch, M. C., Lofrano Alves, M. S., Guimaraes, G. V., Issa, V. S., … Bocchi, E. A. (2018). Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity: The CECCY Trial. *Journal of the American College of Cardiology*, *71*(20), 2281–2290. https://doi.org/10.1016/j.jacc.2018.02.049

Bianco, C. M., Al-Kindi, S. G., & Oliveira, G. H. (2017). Advanced Heart Failure Therapies for Cancer Therapeutics–Related Cardiac Dysfunction. *Heart Failure Clinics*, *13*(2), 327–336. https://doi.org/10.1016/j.hfc.2016.12.005

Boehringer Ingelheim. (2014, August). *FDA approves Jardiance® (empagliflozin) tablets for adults with type 2 diabetes* [Text]. Boehringer-Ingelheim.Us. https://www.boehringer-ingelheim.us/press-release/fda-approves-jardiance-empagliflozin-tablets-adults-type-2-diabetes

Cardinale Daniela, Colombo Alessandro, Bacchiani Giulia, Tedeschi Ines, Meroni Carlo A., Veglia Fabrizio, Civelli Maurizio, Lamantia Giuseppina, Colombo Nicola, Curigliano Giuseppe, Fiorentini Cesare, & Cipolla Carlo M. (2015). Early Detection of Anthracycline Cardiotoxicity and Improvement With Heart Failure Therapy. *Circulation*, *131*(22), 1981–1988. https://doi.org/10.1161/CIRCULATIONAHA.114.013777

Dalen, E. C. van, Caron, H. N., Dickinson, H. O., & Kremer, L. C. (2011). Cardioprotective interventions for cancer patients receiving anthracyclines. *Cochrane Database of Systematic Reviews*, *6*. https://doi.org/10.1002/14651858.CD003917.pub4

Fitchett, D., Zinman, B., Wanner, C., Lachin, J. M., Hantel, S., Salsali, A., Johansen, O. E., Woerle, H. J., Broedl, U. C., Inzucchi, S. E., & EMPA-REG OUTCOME® trial investigators. (2016). Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: Results of the EMPA-REG OUTCOME® trial. *European Heart Journal*, *37*(19), 1526–1534. https://doi.org/10.1093/eurheartj/ehv728

Gallo, L. A., Wright, E. M., & Vallon, V. (2015). Probing SGLT2 as a therapeutic target for diabetes: Basic physiology and consequences. *Diabetes and Vascular Disease Research*, *12*(2), 78–89. https://doi.org/10.1177/1479164114561992

Green, C. P., Porter, C. B., Bresnahan, D. R., & Spertus, J. A. (2000). Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: A new health status measure for heart failure. *Journal of the American College of Cardiology*, *35*(5), 1245–1255. https://doi.org/10.1016/s0735-1097(00)00531-3

Henriksen, P. A. (2018). Anthracycline cardiotoxicity: An update on mechanisms, monitoring and prevention. *Heart*, *104*(12), 971–977. https://doi.org/10.1136/heartjnl-2017-312103

Hicks, K. A., Mahaffey, K. W., Mehran, R., Nissen, S. E., Wiviott, S. D., Dunn, B., Solomon, S. D., Marler, J. R., Teerlink, J. R., Farb, A., Morrow, D. A., Targum, S. L., Sila, C. A., Thanh Hai, M. T., Jaff, M. R., Joffe, H. V., Cutlip, D. E., Desai, A. S., Lewis, E. F., … Pocock, S. J. (2018). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Journal of the American College of Cardiology*, *71*(9), 1021–1034. https://doi.org/10.1016/j.jacc.2017.12.048

Lan, N. S. R., Fegan, P. G., Yeap, B. B., & Dwivedi, G. (2019). The effects of sodium-glucose cotransporter 2 inhibitors on left ventricular function: Current evidence and future directions. *Esc Heart Failure*, *6*(5), 927–935. https://doi.org/10.1002/ehf2.12505

Macedo, A. V. S., Hajjar, L. A., Lyon, A. R., Nascimento, B. R., Putzu, A., Rossi, L., Costa, R. B., Landoni, G., Nogueira-Rodrigues, A., & Ribeiro, A. L. P. (2019). Efficacy of Dexrazoxane in Preventing Anthracycline Cardiotoxicity in Breast Cancer. *JACC: CardioOncology*, *1*(1), 68–79. https://doi.org/10.1016/j.jaccao.2019.08.003

Maurea, N., Quagliariello, V., Coppola, C., Rea, D., Barbieri, A., Arra, C., & Botti, G. (2019). Empaglifozin has cardioprotective and anti-inflammatory effects during doxorubicin treatment: A preclinical study. *Journal of Clinical Oncology*, *37*(15_suppl), e23057–e23057. https://doi.org/10.1200/JCO.2019.37.15_suppl.e23057

Miller, K. D., Siegel, R. L., Lin, C. C., Mariotto, A. B., Kramer, J. L., Rowland, J. H., Stein, K. D., Alteri, R., & Jemal, A. (2016). Cancer treatment and survivorship statistics, 2016. *CA: A Cancer Journal for Clinicians*, *66*(4), 271–289. https://doi.org/10.3322/caac.21349

Oh, C.-M., Cho, S., Jang, J.-Y., Kim, H., Chun, S., Choi, M., Park, S., & Ko, Y.-G. (2019). Cardioprotective Potential of an SGLT2 Inhibitor Against Doxorubicin-Induced Heart Failure. *Korean Circulation Journal*, *49*(12), 1183–1195. https://doi.org/10.4070/kcj.2019.0180

Packer, M. (2019). Lessons learned from the DAPA-HF trial concerning the mechanisms of benefit of SGLT2 inhibitors on heart failure events in the context of other large-scale trials nearing completion. *Cardiovascular Diabetology*, *18*(1), 129. https://doi.org/10.1186/s12933-019-0938-6

Packer, M., Anker, S. D., Butler, J., Filippatos, G., & Zannad, F. (2017). Effects of Sodium-Glucose Cotransporter 2 Inhibitors for the Treatment of Patients With Heart Failure: Proposal of a Novel Mechanism of Action. *JAMA Cardiology*, *2*(9), 1025–1029. https://doi.org/10.1001/jamacardio.2017.2275

Payne, D. L., & Nohria, A. (2017). Prevention of Chemotherapy Induced Cardiomyopathy. *Current Heart Failure Reports*, *14*(5), 398–403. https://doi.org/10.1007/s11897-017-0353-9

Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., Falk, V., González-Juanatey, J. R., Harjola, V.-P., Jankowska, E. A., Jessup, M., Linde, C., Nihoyannopoulos, P., Parissis, J. T., Pieske, B., Riley, J. P., Rosano, G. M. C., Ruilope, L. M., Ruschitzka, F., … ESC Scientific Document Group. (2016). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*, *37*(27), 2129–2200. https://doi.org/10.1093/eurheartj/ehw128

Quade, D. (1967). Rank Analysis of Covariance. *Journal of the American Statistical Association*, *62*(320), 1187–1200. JSTOR. https://doi.org/10.2307/2283769

Quagliariello, V., Coppola, C., Rea, D., Maurea, C., Barbieri, A., Botti, G., & Maurea, N. (2019). 1894P - Cardioprotective and anti-inflammatory effects of empagliflozin during treatment with doxorubicin: A cellular and preclinical study. *Annals of Oncology*, *30*, v768. https://doi.org/10.1093/annonc/mdz268.021

Sawyer, D. B. (2013, March 20). *Anthracyclines and Heart Failure* [Review-article]. Http://Dx.Doi.Org.Proxy1.Library.Jhu.Edu/10.1056/NEJMcibr1214975. https://doi.org/10.1056/NEJMcibr1214975

Siegel, R., DeSantis, C., Virgo, K., Stein, K., Mariotto, A., Smith, T., Cooper, D., Gansler, T., Lerro, C., Fedewa, S., Lin, C., Leach, C., Cannady, R. S., Cho, H., Scoppa, S., Hachey, M., Kirch, R., Jemal, A., & Ward, E. (2012). Cancer treatment and survivorship statistics, 2012. *CA: A Cancer Journal for Clinicians*, *62*(4), 220–241. https://doi.org/10.3322/caac.21149

Soloveva, A., Villevalde, S., & Kobalava, Z. (2017). P4231Cardiorenohepatic syndrome reflects severity of decompensated heart failure and is related with worse prognosis. *European Heart Journal*, *38*(suppl_1). https://doi.org/10.1093/eurheartj/ehx504.P4231

Spalato Ceruso, M., Napolitano, A., Silletta, M., Mazzocca, A., Valeri, S., Improta, L., Santini, D., Tonini, G., Badalamenti, G., & Vincenzi, B. (2019). Use of Cardioprotective Dexrazoxane Is Associated with Increased Myelotoxicity in Anthracycline-Treated Soft-Tissue Sarcoma Patients. *Chemotherapy*, *64*(2), 105–109. https://doi.org/10.1159/000501195

Sturgeon, K. M., Deng, L., Bluethmann, S. M., Zhou, S., Trifiletti, D. M., Jiang, C., Kelly, S. P., & Zaorsky, N. G. (2019). A population-based study of cardiovascular disease mortality risk in US cancer patients. *European Heart Journal*, *40*(48), 3889–3897. https://doi.org/10.1093/eurheartj/ehz766

Swain, S. M., Whaley, F. S., & Ewer, M. S. (2003). Congestive heart failure in patients treated with doxorubicin. *Cancer*, *97*(11), 2869–2879. https://doi.org/10.1002/cncr.11407

Tentolouris, A., Vlachakis, P., Tzeravini, E., Eleftheriadou, I., & Tentolouris, N. (2019). SGLT2 Inhibitors: A Review of Their Antidiabetic and Cardioprotective Effects. *International*

Journal of Environmental Research and Public Health, *16*(16), 2965. https://doi.org/10.3390/ijerph16162965

Timm, K. N., & Tyler, D. J. (2020). The Role of AMPK Activation for Cardioprotection in Doxorubicin-Induced Cardiotoxicity. *Cardiovascular Drugs and Therapy*. https://doi.org/10.1007/s10557-020-06941-x

Vaduganathan, M., & Januzzi, J. L. (2019). Preventing and Treating Heart Failure with Sodium-Glucose Co-Transporter 2 Inhibitors. *The American Journal of Cardiology*, *124 Suppl 1*, S20–S27. https://doi.org/10.1016/j.amjcard.2019.10.026

van der Meer, P., Gaggin, H. K., & Dec, G. W. (2019). ACC/AHA Versus ESC Guidelines on Heart Failure: JACC Guideline Comparison. *Journal of the American College of Cardiology*, *73*(21), 2756–2768. https://doi.org/10.1016/j.jacc.2019.03.478

Vejpongsa, P., & Yeh, E. T. H. (2014). Prevention of Anthracycline-Induced Cardiotoxicity: Challenges and Opportunities. *Journal of the American College of Cardiology*, *64*(9), 938–945. https://doi.org/10.1016/j.jacc.2014.06.1167

Wang, D., & Pocock, S. (2016). A win ratio approach to comparing continuous non-normal outcomes in clinical trials. *Pharmaceutical Statistics*, *15*(3), 238–245. https://doi.org/10.1002/pst.1743

Yancy Clyde W., Jessup Mariell, Bozkurt Biykem, Butler Javed, Casey Donald E., Drazner Mark H., Fonarow Gregg C., Geraci Stephen A., Horwich Tamara, Januzzi James L., Johnson Maryl R., Kasper Edward K., Levy Wayne C., Masoudi Frederick A., McBride Patrick E., McMurray John J.V., Mitchell Judith E., Peterson Pamela N., Riegel Barbara, … Wilkoff

Bruce L. (2013). 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Circulation*, *128*(16), e240–e327. https://doi.org/10.1161/CIR.0b013e31829e8776

Zamorano, J. L., Lancellotti, P., Rodriguez Muñoz, D., Aboyans, V., Asteggiano, R., Galderisi, M., Habib, G., Lenihan, D. J., Lip, G. Y. H., Lyon, A. R., Lopez Fernandez, T., Mohty, D., Piepoli, M. F., Tamargo, J., Torbicki, A., Suter, T. M., Zamorano, J. L., Aboyans, V., Achenbach, S., … Windecker, S. (2016). 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *European Heart Journal*, *37*(36), 2768–2801. https://doi.org/10.1093/eurheartj/ehw211

Zelniker, T. A., Wiviott, S. D., Raz, I., Im, K., Goodrich, E. L., Bonaca, M. P., Mosenzon, O., Kato, E. T., Cahn, A., Furtado, R. H. M., Bhatt, D. L., Leiter, L. A., McGuire, D. K., Wilding, J. P. H., & Sabatine, M. S. (2019). SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials. *The Lancet*, *393*(10166), 31–39. https://doi.org/10.1016/S0140-6736(18)32590-X

Zhang, S., Liu, X., Bawa-Khalfe, T., Lu, L.-S., Lyu, Y. L., Liu, L. F., & Yeh, E. T. H. (2012). Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nature Medicine*, *18*(11), 1639–1642. https://doi.org/10.1038/nm.2919

Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., Mattheus, M., Devins, T., Johansen, O. E., Woerle, H. J., Broedl, U. C., Inzucchi, S. E., & EMPA-REG OUTCOME Investigators. (2015). Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2

Diabetes. *The New England Journal of Medicine*, *373*(22), 2117–2128.

https://doi.org/10.1056/NEJMoa1504720

END