An interdisciplinary ecosystem for the psychosocial and behavioural management of Cardiotoxicity in elderly breast cancer patient: a prospective clinical study

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Abstract

Background: Over 50% of newly diagnosed breast cancer patients are 65+ years old. Due to age-related factors and the presence of comorbidities, these patients are particularly vulnerable to developing cardiac toxicity associated with cancer treatments, which may lead to suboptimal interventions and undertreatment, resulting in poorer health outcomes, Quality of Life (QoL) deterioration and increased healthcare costs. Given the underrepresentation of elderly breast cancer patients in clinical trials and the increasing recognition of psycho-social and behavioural factors' impact on cardiovascular (CV) disease onset, broader and interdisciplinary studies are required to develop new and innovative best practices for this clinical population.

Objective: Using an innovative eHealth approach combining the CARDIOCARE (CARDIOCARE – "An Interdisciplinary Approach for the Management of the Elderly Multimorbid Patient with Breast Cancer Therapy Induced Cardiac Toxicity" – Grant Agreement 945175) Mobile App and technologically advanced wearable devices (i.e., the Garmin Venu SQ watch and the Polar h10), the CARDIOCARE prospective study pursues a twofold aim: 1) testing the effectiveness of the CARDIOCARE mobile App to monitor and assess elderly breast cancer patients' intrinsic capacity and QoL and evaluating CARDIOCARE eHealth interventions effectiveness on these parameters 2) developing a holistic, patient-centred risk prediction model, specific for the detection of cardiotoxicity before it clinically emerges.

Methods: The study is prospective and multicentric and involves six clinical and five technical partners across Europe. Seven hundred fifty elderly breast cancer patients (? 60years old) are randomised into either the intervention group or the control arm, with only patients in the former receiving access to eHealth psychological, behavioural, and functional interventions implemented on the CARDIOCARE eHealtHeart App. Patients will be recruited in the six clinical centres and will undergo clinical procedures to collect multi-modal data including clinical data, cardiac imaging, biochemical and psychological biomarkers and omics, intrinsic capacity, and QoL indicators, measured at baseline (T0) and every three months, up to 12 months (T5).

Results: CARDIOCARE is a project funded by Horizon 2020 and enrollment (WP4) started in May 2023. Recruitment and first data analysis are currently underway.

Conclusions: The CARDIOCARE prospective study will contribute to developing new best practice guidelines for managing elderly multimorbid breast cancer patients while preserving their intrinsic capacity and improving their QoL. Furthermore, the CARDIOCARE Mobile App and the wearable devices will allow clinicians to identify trajectories across the cardiotoxicity disease continuum and thus intervene in a preventative way on higher-risk patients. Such a healthcare approach will also benefit the healthcare system, which currently spends almost 40% of its resources on patients over 60, with long-term care and hospital admissions being the primary cost drivers. Clinical Trial: NCT06334445

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AN INTERDISCIPLINARY ECOSYSTEM FOR THE PSYCHOSOCIAL AND BEHAVIOURAL MANAGEMENT OF CARDIOTOXICITY IN ELDERLY BREAST CANCER PATIENT: A PROSPECTIVE CLINICAL STUDY

ABSTRACT

Background: Over 50% of newly diagnosed breast cancer patients are 65+ years old. Due to age-related factors and the presence of comorbidities, these patients are particularly vulnerable to developing cardiac toxicity associated with cancer treatments, which may lead to suboptimal interventions and undertreatment, resulting in poorer health outcomes, Quality of Life (QoL) deterioration and increased healthcare costs. Given the underrepresentation of elderly breast cancer patients in clinical trials and the increasing recognition of psycho-social and behavioural factors' impact on cardiovascular (CV) disease onset, broader and interdisciplinary studies are required to develop new and innovative best practices for this clinical population.

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Results: CARDIOCARE is a project funded by Horizon 2020 and enrollment (WP4) started in May 2023. Recruitment and first data analysis are currently underway.

Conclusions: The CARDIOCARE prospective study will contribute to developing new best practice guidelines for managing elderly multimorbid breast cancer patients while preserving their intrinsic capacity and improving their QoL. Furthermore, the CARDIOCARE Mobile App and the wearable devices will allow clinicians to identify trajectories across the cardiotoxicity disease continuum and thus intervene in a preventative way on higher-risk patients. Such a healthcare approach will also benefit the healthcare system, which currently spends almost 40% of its resources on patients over 60, with long-term care and hospital admissions being the primary cost drivers.

Trial Registration: NCT06334445

KEYWORDS: breast cancer; elderly; cardiotoxicity; prospective study; eHealth; mobile application; risk prediction model

INTRODUCTION

Over 50% of newly diagnosed breast cancer patients are older than 65 and are particularly vulnerable to the cardiotoxic effects of cancer treatment and the onset of multiple comorbidities due to age-related risk factors (Reddy et al., 2017; Singh et al., 2018). The cumulative effect of risk factors in the elderly breast cancer patient resembles a “snowball effect”, where baseline age-related risk factors and cancer-related changes are further exacerbated by direct therapy-induced cardiotoxicity (Carioli et al., 2020; Montazeri et al., 2014), resulting in severe multimorbid conditions and mortality. Underestimating the cardiotoxicity risk in this vulnerable population may lead to inappropriate interventions and undertreatment, resulting in poorer health outcomes, Quality of Life (QoL) deterioration, and increased healthcare costs. Considering that elderly cancer patients are systematically underrepresented in clinical trials (Reddy et al., 2017), there are currently limited means to effectively address the complex needs of these patients and their caregivers, often resulting in undertreatment and suboptimal health outcomes, with negative consequences on patients’ QoL (Reddy et al., 2017). Therefore, in line with the World Health Organisation’s view that health is a state of complete physical, mental, and social well-being (World Health Organization, 2006), broader, interdisciplinary, and patient-oriented clinical trials able to provide new evidence-based best practices for managing elderly breast cancer patients are urgently needed. To date, the most effective approach to minimize cardiotoxicity is early detection and early onset of prophylactic treatment. However, although advances have been made in the detection and management of cardiac toxicity based on imaging techniques (i.e., 2D and 3D Echocardiography and cardiac MRI - Magnetic Resonance Imaging), such instruments lack the sensitivity to detect subclinical changes, and indeed detect cardiac toxicity only once a functional impairment emerges, precluding any chance of effective prevention.

Moreover, psychological conditions such as depression, distress, and anxiety - often observed in cancer patients after diagnosis (Mohamed et al., 2017) - can increase the risk of cardiovascular complications (Bussotti and Sommalunga, 2018). Furthermore, people presenting negative affectivity and social inhibition are exposed to a higher risk of cardiovascular disease than those not presenting such personality assets and that this kind of negative affectivity is significantly associated with higher systolic and diastolic blood pressure (Denollet et al. 2003; Lin et al. 2020). Similarly, prolonged exposure to stressful life circumstances may predict subsequent hypertension and cardiovascular disease (Rosengren et al., 2004). Therefore, the Integrated Care for Older People (ICOPE) guidelines recommend that ECGs and biomarkers (e.g., troponin I, BNP) assessments, as well as a detailed evaluation of patients’ intrinsic capacity - defined as their overall physical and psycho-social characteristics - are included in a gold-standard follow-up protocol to establish new, holistic, and patient-oriented best practices for the management of elderly cancer patients at risk of cardiotoxic effects associated with

oncological treatments (Chianca et al., 2022).

NOVELTY AND STUDY AIM

So far, no extensive studies have allowed the collection of all necessary data to create a meaningful assessment of elderly breast cancer patients' intrinsic capacity and QoL. Thus, the CARDIOCARE prospective study will adopt technologically advanced tools to collect a large amount of data on elderly breast cancer patients' physical, psycho-social, and behavioural parameters to better identify patients at risk of developing cardiotoxicity due to oncological treatments and improve their psychological and physical well-being during and after their oncological care pathway.

Since August 2021, a CARDIOCARE retrospective study has been running with breast cancer patients aged ≥ 65 with and without cardiovascular diseases at baseline (T0) and patients ≥ 55 with a breast cancer diagnosis and cardiac damage and toxicity before starting any active treatment for breast cancer. Multimodal retrospective data have been retrieved from existing databases in five of the six clinical centres belonging to the CARDIOCARE consortium (BOCOC, IEO, KSBC, NKUA, and UOI), to develop a risk prediction model for cardiotoxicity in the elderly breast cancer population to be refined and validated through the CARDIOCARE prospective study. In the prospective study, the cardiotoxicity risk prediction model will be enriched with novel biochemical, -omics (metagenomics, microRNA (miRNAs), Single Nucleotide Polymorphisms (SNPs)), and psychological markers to better assess how patients' intrinsic capacity (physical and mental) and QoL are affected by cancer and anticancer treatments and how they influence the risk of developing cardiac toxicity. Furthermore, the CARDIOCARE prospective study will be the first one to observe, in a clinical study setting, how the gut microbiome of elderly breast cancer patients is affected by different oncological treatments, and if any association exists between the gut microbiome, cardiac toxicity etiopathogenesis and intrinsic capacity, paving the way for future potential biotic treatments.

OBJECTIVE(S) AND RATIONALE

- Stratify patients aged ≥ 60 with breast cancer based on their risk of developing cardiotoxicity.

  Rationale: So far, multiple studies have explored the effects of specific risk factors; however, these have yet to deal comprehensively with the impact of clinical, biological, psychological, and behavioural risk factors and their interactions.
- Evaluate the effects of eHealth psychological and behavioural interventions on elderly breast cancer patients' intrinsic capacity and QoL and on their risk of developing cardiac toxicity.

  Rationale: Although recent studies associate psychosocial and behavioural characteristics with the risk of developing cardiovascular diseases, these studies on elderly patients with breast cancer are still limited (Pedersen et al. 2017). However, gaining such knowledge is necessary to generate hypotheses on using eHealth interventions to support this clinical population.

METHODS

STUDY DESIGN AND PARTNERS

The CARDIOCARE prospective study is multicentric and involves six European clinical partners: the European Institute of Oncology (IEO) - the study clinical coordinator - in Italy, the Bank of Cyprus Oncology Centre (BOCOC) in Cyprus, the Karolinska University Hospital (KSBC) in Sweden, the University of Ioannina (UOI) and the National and Kapodistrian University of Athens (NKUA) in Greece, and the Institute of Oncology Ljubiana (IOL) in Slovenia. The work of these clinical centres and especially the technological aspects of eHealth tools implementation is supported by five European technical partners: the Foundation for Research and Technology (FORTH), the Hellenic Mediterranean University (HMU) and the University of Ioannina (UOI), all based in Greece, a Head of Research and Development Company (STREMBLE) in Cyprus, , the European Society of Cardiology (ESC) based in France, and the Philips Electronics BV (PHILIPS) in the Netherland. Part of the CARDIOCARE consortium is also the Institute of Health Management (IMS) in Italy, ensuring the highest study conduct and management quality.

This multicenter clinical study has been designed as a prospective observational study that examines whether integrated patient-oriented psychological, behavioural, and functional interventions can prevent, delay, or mitigate cardiotoxicity as an adverse effect of cancer therapy. It will include 750 elderly breast cancer patients recruited across the participating clinical centres (IEO: 125, BOCOC: 120, KSBC: 125, UOI: 60, NKUA: 195, IOL: 125). A subsample of 500 patients will be randomly selected (IEO: 100, BOCOC: 100, KSBC: 80, NKUA: 130, IOL: 90) to allow STREMBLE to assess gut microbiome changes associated with oncological treatments.

All recruited patients will be randomly assigned to either the study's intervention or control arms. Patients in both arms, in addition to standard oncological care, will receive eHealth monitoring through the Garmin Venu SQ Smart Watch and the Polar h10, technologically advanced wearable devices (described in detail in Section 3.4. - "Instruments and measures") and will have access to the ePsycHeart assessment tool on the CARDIOCARE Mobile App (described in detail in the "Instruments and measures" section). Furthermore, patients will be given a Motorola smartphone on which the CARDIOCARE Mobile app is installed. These technological instruments will provide clinicians with the patient's physical and psychological intrinsic capacity and QoL indicators foreseen by the study protocol. However, only patients in the intervention arm will have access to the behavioural, psychological, functional, and educational interventions in the eHealtHeart section of the CARDIOCARE Mobile App, which will allow researchers to evaluate the effectiveness of such eHealth interventions on elderly breast cancer patients' intrinsic capacity and QoL, as well as these interventions' effectiveness in mitigating, delaying, or even preventing the onset of cardiac toxicity associated with breast cancer treatments.

Patients will be randomised through the study electronic Case Report Form (eCRF) at baseline and assigned to the intervention or control arm in a 1:1 ratio. The study time points, follow-ups, and specific procedures are detailed in section 3.5 – "Study time points and procedures".

STUDY PARTICIPANTS

A total of 750 women aged ≥ 60 with a diagnosis of breast cancer will be recruited across the six European clinical centres involved in the CARDIOCARE consortium in Italy, Greece, Cyprus, Sweden, and Slovenia. Details on the inclusion and exclusion criteria to recruit patients are provided in section 3.3 below - “Selection Criteria”.

SELECTION CRITERIA

INCLUSION CRITERIA

1. Women ≥ 60 years with a diagnosis of early/locoregional breast cancer who will undergo neoadjuvant and/or adjuvant treatment with regimens including anthracyclines and/or taxanes.
2. Women ≥ 60 years with a diagnosis of HER2-positive early/locoregional breast cancer who will undergo neoadjuvant and/or adjuvant treatment with anti-HER2 therapy (trastuzumab or trastuzumab and pertuzumab).
3. Women ≥60 years with a diagnosis of early/locoregional breast cancer who will undergo neoadjuvant and/or adjuvant treatment with endocrine therapies +/- CDK 4/6 inhibitors.
4. Women ≥ 60 years with HER2-positive metastatic breast cancer who will undergo first-line therapy with anti-HER2 therapy (trastuzumab or trastuzumab and pertuzumab +/- chemotherapy).
5. Women with age ≥ 60 years before starting the aforementioned treatment for breast cancer.
6. Women eligible ≥ 60 years who will undergo first-line therapy in the metastatic setting with any type of treatment (chemotherapy, immunotherapy, biological agents).
7. Willingness and ability to comply with scheduled visits, laboratory tests, and other trial procedures.
8. Able to understand provided information and can provide written informed consent.
9. Participant affiliated to a social security system.
10. Life expectancy of at least 12 months.

EXCLUSION CRITERIA

1. Age < 60 years.
2. Diagnosed severe psychiatric or neurological disorders that might impair the ability to give informed consent.

INSTRUMENTS AND MEASURES

All recruited patients will receive additional supportive care in conjunction with standard care. Patients in the intervention arm and those in the control arm of the study will receive wearable devices and complete an initial evaluation on the CARDIOCARE mobile App.

THE CARDIOCARE MOBILE APP

The CARDIOCARE Mobile App is installed on the Motorola smartphone provided to patients, which they will have to return after use. The CARDIOCARE App allows access to two different settings containing specific modules (described here under), depending upon the group - control or intervention - the patient is assigned to.

As foreseen by the intervention vs. control design of the study, the Cognitive Stimulation, the Education and Training, the Vision and Hearing, and the Psychology and Well-being (except for the Questionnaires submodule) modules will only be accessed by the intervention arm of the study.

The 6 modules are: 1) Mobility and Vitality; 2) Cognitive Stimulation; 3) Education and Training; 4) the Geriatric Syndrome Assessment; 5) Vision and Hearing; and 6) Psychology and Wellbeing.

The Mobility and Vitality module contains 4 submodules, which are the Nutrition Questionnaire, the Physical Activity, the Cardio Recording Session (CRS), and the Hand Grip Session (HGS). Together, these submodules will provide a collection of graphs - such as bar and pie charts - representing data on the patient's overall functional well-being, sleep duration, physical activities, average heart rate, as well as proxies of the patient's stress levels.

The Cognitive Stimulation module includes 4 cognitive games, which are "Find the Word", "Tic Tac Toe", "Color Beans", and "Drawing". If played consistently, such games can foster the patient's attention, concentration, and working memory capacities, therefore counteracting the cognitive impairment often found in patients undergoing oncological treatments.

The Education and Training module includes 2 submodules: the first one is the "Breast Cancer Material" which contains patient-oriented information related to breast cancer and cardiotoxicity and on the potential psychological and social implications breast cancer and its treatment can have. This submodule provides a deeper awareness about the clinical implications of the disease and guidance for the patients to preserve their psychological well-being. The second submodule is named "Training" and contains a video tutorial for patients to improve their balance and reinforce their muscles' strength.

The Geriatric Syndrome Assessment module includes 2 submodules: the first one is the "Incontinence Management", which will allow each patient to report urination incidents, perform guided exercises for pelvic floor strengthening, and set reminders for toilet usage; the second one is the "Falls Mitigation" submodule, where the patient can access the OTAGO programme, a set of exercises designed to help them enhance and restore their balance (Shubert et al. 2017).

The Vision and Hearing module includes the Vision Test and the Hearing Test submodules: the first is an assessment of the patient's vision capacity that was designed based on the Snellen test guidelines; the second one is an assessment of the patient's hearing capability designed based on the Whisper test guidelines.

Lastly, the Psychology and Wellbeing module includes behavioural and psychological interventions corresponding to 5 submodules: the Expressive Writing (EW), the Best Possible Self (BPS), the ABCDE (A = Activating event or situation; B = Beliefs; C = Consequences; D =

Disputation of beliefs; E = Effective new approach), and the Biofeedback Session. Such interventions aim to mitigate the psychological risk factors associated with cardiotoxicity development and deterioration of the patient's quality of life. The fifth submodule is the Questionnaires one, which includes 15 self-reported measures that will provide critical information on the patient's levels of perceived stress, resilience, anxiety and depression, self-management and emotion regulation capacity, coping skills, perceived social support, satisfaction with and quality of life, as well as their levels of optimism.

THE WERABLE DEVICES

The CARDIOCARE mobile App, described above, will process data deriving from two technologically advanced wearable devices: the Garmin Venu SQ watch and the Polar h10. The Garmin Venu SQ watch will collect data on the patient's heart rate (resting, high), body battery (percentage, charged, drained), stress (rest, low, med, high), intensity minutes (per week, today, goal), steps (today, goal), calories (total today, resting, active), and respiration (brpm, sleep avg, awake avg). The Polar h10 is a chest strap measuring highly detailed and accurate information about the patient's heart rate and ECG.

The patient is required to wear the Garmin Venu SQ all the time (day and night) for the first six months of the study and to wear the Polar h10 for around 30 minutes every two weeks. At the end of month 6 of the study (T3), each patient must return the three wearable devices to their clinical centre.

Patients will also be asked to use, at T1 and T3, the hand grip dynamometer, to assess their hand grip strength during their cardiological or oncological visit.

STUDY TIME POINTS AND PROCEDURES

As per protocol, before undertaking any study procedure, the patient will receive the Patient Information Sheet, where the different study procedures are explained in lay-public language. The same document also sets out the study's risks, benefits, and aims. Once the patient has read the Patient Information Sheet and has received answers to any questions or concerns, she can choose to provide her Informed Consent to participate in the study by signing the Written Informed Consent form, of which she will be left a copy, while the CARDIOCARE researchers will keep the original document. After the patient has signed the written Informed Consent form, she will follow the study procedures set for each time point, as shown in Table 1 (Study time points and procedures scheduled).

In the screening phase (T0), after receiving the patient's Informed Consent, each patient will undergo a screening procedure, during which demographic information and additional information on the Personal and Family Medical History, will be collected for all patients. Adherence to inclusion/exclusion criteria will be verified. In addition, plasma troponin I level assessment (if possible) and cardiological visit (if needed) will be performed.

At baseline, before starting treatment (T1), the following clinical and logistical procedures will be performed: the oncological visit, the cardiological visit (if needed), the psychological visit and the cognitive assessment (if the center has specialised personnel), collection of information

on smoking habits, Blood Pressure (BP) and Heart Rate (HR) measurement, the routine blood analyses (i.e., hematology and biochemistry), ECHO assessment, ECG assessment, mammography, plasma troponin I level assessment (if not already taken at T0), Plasma Brain Natriuretic Peptide (BNP) assessment, plasma myeloperoxidase and high-sensitivity C-Reactive Protein (CRP) assessment (if possible), the plasma and stool samples collection for miRNA analyses, the blood sample collection for genetic analyses, the development of the oncological treatment plan, the revision of concomitant prescriptions, a brief training on the use of the Mobile App and wearable devices, the Gastrointestinal Symptom Rating Score (GSRS) assessment, the Patient Lifestyle questionnaire completion, the self-administered scales completion check, the hand-grip test, and the adverse events (AEs) assessment.

At Treatment start (Day 0), patients will start an oncological treatment cycle. Concomitant medications and information on Adverse Events will be collected. In addition, the self-administered scales completion check will be performed.

At month 3 (T2 follow-up), the following procedures will be performed: the cardiological visit (if needed), the psychological visit (if the centre has specialised personnel), the BP and HR measurement, ECHO assessment, ECG assessment, routine blood analyses (i.e., haematology and biochemistry), the plasma troponin I level assessment, the plasma BNP assessment, the plasma myeloperoxidase and high-sensitivity CRP assessment (if available), the oncological treatment status (ongoing/completed) check, the information on treatment status (ongoing/completed) check, the concomitant medication check, the self-administered scales completion check, the data collected by the wearable devices check, and the AEs assessment. At month 6 of the study (T3 follow-up), the following procedures will be performed: the oncological visit, the cardiological visit (if needed), the psychological visit and the cognitive assessment (if the centre has specialised personnel), the BP and HR measurement, ECHO assessment, ECG assessment, the routine blood analyses (i.e., haematology and biochemistry), the plasma troponin I level assessment, the plasma BNP assessment, the plasma myeloperoxidase and high-sensitivity CRP assessment (if available), the oncological treatment status check, the information on treatment status (ongoing/completed) check, the information on the patient's out-of-pocket expenses, the concomitant medications check, the self-administered scales completion check, the data collected by the wearable devices check, the hand-grip test, and the AEs assessment.

At month 9 of the study (T4 follow-up), the following procedures will be performed: the cardiological visit (if needed and if possible), the psychological visit (if the centre has specialised personnel and if possible), the BP and HR measurement (if possible), ECHO assessment (if possible), ECG assessment (if possible), routine blood analyses (i.e., haematology and biochemistry), the plasma troponin I level assessment, the plasma BNP assessment, the plasma myeloperoxidase and high-sensitivity CRP assessment (if available), the oncological treatment status (ongoing/completed) check, the information on treatment status (ongoing/completed) check, the concomitant medication check (if possible), the self-administered scales completion check (paper-based), and the AEs assessment.

At month 12 of the study (T5 follow-up), the following procedures will be performed: the oncological visit, the cardiological visit (if needed), the psychological visit and the cognitive assessment (if the centre has specialised personnel), the BP and HR measurement, ECHO

assessment, ECG assessment, mammography, the routine blood analyses (i.e., haematology and biochemistry), the plasma troponin I level assessment, the plasma BNP assessment, the plasma myeloperoxidase and high-sensitivity CRP assessment (if available), the oncological treatment status check, the information on treatment status (ongoing/completed) check, the information on the patient's out-of-pocket expenses, the self-administered scales completion check (paper-based), the concomitant medications check, the hand-grip test, and the AEs assessment.

Finally, 14 to 25 days after the end of treatment, clinical investigators will collect information on patient's smoking habits, their GSRS assessment, and the Patient Lifestyle questionnaire completion. They will also collect the patient's stool and plasma samples for miRNA analyses, information on the patient's oncological treatment plan, changes and/or cycles, information on concomitant medications and, finally, will perform the last AEs assessment.

Table 1. Summary of procedures scheduled

Procedure	May be one single or two visits		Day 0	Month 3	Month 6	Month 9	Month 12	14-25 days after the end of treatment***
	Day -15 T0 (screening)	T1 (baseline)	Treatment start	T2	T3	T4	T5	Tn
ICF signature	X							
Diagnosis	X							
Personal and Family Medical History (Including diagnosis of severe psychiatric disorders)	X							
Smoking habits		X						X
Co-morbidities	X							
Oncological visit		X			X		X	
Psychological visit ¥ (if the center has a psychological support service)		X		X	X	X§	X	
Cardiological visit (if needed)	X	X		X	X	X§	X	
BP and HR measurement		X		X	X	X§	X	
Routine blood analysis (i.e.,		X		X	X	X	X	

Procedure	May be one single or two visits		Day 0	Month 3	Month 6	Month 9	Month 12	14-25 days after the end of treatment***
	Day -15 T0 (screening)	T1 (baseline)	Treatment start	T2	T3	T4	T5	Tn
hematology and biochemistry) *								
ECHO assessment**		X		X	X	X§	X	
ECG assessment		X		X	X	X§	X	
Plasma troponin I level assessment	X&	X&		X	X	X	X	
Mammography (if patient did not undergo mastectomy)		X					X	
Plasma BNP assessment		X		X	X	X	X	
Plasma myeloperoxidase and high-sensitivity CRP (if available)		X		X	X	X	X	
I/E checklist	X							
Collect blood sample for genetic analysis		X						
Collect plasma sample for miRNA analysis		X						X
Collect stool sample		X						X
Oncological treatment (plan/changes), cycle			X	X	X	X	X	X
Information on treatment status (ongoing/completed)				X	X	X	X	
Concomitant medications	X	X	X	X	X	X§	X	X
Gastrointestinal		X						X

Procedure	May be one single or two visits		Day 0	Month 3	Month 6	Month 9	Month 12	14-25 days after the end of treatment***
	Day -15 T0 (screening)	T1 (baseline)	Treatment start	T2	T3	T4	T5	Tn
Symptom Rating Score (GSRS)								
Patient Lifestyle questionnaire		X						X
Verify completion of self-administered scales/questionnaires (ePsycHeart App) #		X	X	X	X	X	X	
Cognitive effect assessment (if the center has specialized personnel)		X			X		X	
Verify collection of data from wearable devices				X	X			
Collect information on patient's out-of-pocket expenses					X		X	
Hand Grip Test		X			X		X	
AE assessment		X	X	X	X	X	X	X

Legend:
ICF: Informed Consent Form
BP: Blood Pressure
HR: Heart Rate
ECHO assessment: Echocardiographic assessment
ECG: Electrocardiogram
I/E checklist: Inclusion/Exclusion criteria checklist
AE: Adverse Events
§ Only if possible.
¥ These visits can be conducted in presence or remotely, if the center can involve the required experts.
The psychological visit consists of meeting the patient in person (if already in the clinical

centre) or remotely to touch base about the study: how they feel about it and whether they would like something to be different / modified. Within the visit, a motivational intervention will also be carried out to minimise drop-outs as much as possible.
* Including cholesterols, glucose levels and renal and liver function tests, if available: IL-6, TNF-α, HRV, CRP, Fibrinogen, and Ferritin.
**Including right and left ventricles dimensions and functions and diastolic function.
***at the first visit after the end of each treatment which should be within 14-25 days. The time of these sample collections will vary in relation to the therapeutic schedule of the patient.
Please refer to Table 2 for the precise list of the questionnaires and scales requested at each time point.
& Troponin can be analyzed either at Screening OR at Baseline

RECRUITMENT AND FOLLOW-UP
Patient recruitment started in May 2023.
In October 2023 a new amended version of the protocol (version 1.2) had been approved. The decision to amend the old protocol and create a new version of the Prospective Clinical Study Protocol in the face of emerging new evidence (Booth et al., 2022; Lyon et al. 2022), an amendment was proposed on the definition of cardiotoxicity and on inclusion criteria related to age and treatment. More specifically:

- the identification of cardiotoxicity includes also the so-called MACEs - Major Cardiovascular Adverse Effects, and more specifically the intra-patient assessment of MACEs, taxanes and endocrine therapies +/- CDK 4/6 inhibitors were included among the inclusion criteria,
- the inclusion criteria of age decrease from =>65 to =>60 years of age.

STATISTICAL PROCEDURE

STATISTICAL CONSIDERATIONS ON THE DESIGN

The primary statistical analysis will use an intention-to-treat (ITT) approach. Therefore, all patients involved in the study will be included in the final analysis. However, based on the literature, patients who do not achieve at least three months of follow-up from the start of treatment will not be included in the analysis (Keramida et al., 2019; Sawaya et al., 2011). Results will be presented using descriptive statistics (mean, standard deviation, median and range for continuous variables, and proportions for nominal variables). Patient baseline characteristics will be compared using a two-sample t-test or a nonparametric test for continuous variables, and Pearson's Chi-square test will be used for qualitative variables. All statistical analyses will be performed using two-tailed tests and adopting a 5% significance level. The effect of the interventions on the primary endpoint will be analysed using the Cox proportional hazards model. Point estimates and 95% confidence intervals will be calculated for the hazard ratio of the control group versus the experimental group. Any statistically significant difference between the two groups at baseline will be balanced by the multivariable adjustment. A logistic regression or Cox proportional hazards model will also be used to

evaluate the effect of the interventions on the secondary endpoints in the two groups. Continuous variables, such as those obtained from imaging and biochemical and molecular biomarkers, will be summarised descriptively at baseline and follow-up visits. The differences between the two groups during the different follow-up visits will be evaluated by the analysis of covariance, considering the respective baseline measurement as a covariant.
Finally, for the cost-effectiveness analysis, the health and QoL outcomes that will emerge during the study will be used to calculate the Quality-Adjusted Life-Years (QALYs). The costs will be combined with the QALYs for the cost-utility analysis to estimate the cost-per-QALYs associated with implementing the CARDIOCARE model and the interventions foreseen by it. The Incremental Cost-Effectiveness Ratio (ICER) will also be calculated to evaluate the CARDIOCARE model's effectiveness compared to current care practices. The ICER, which will be calculated using a threshold approach, will therefore allow us to better understand how to distribute and allocate the different healthcare resources.

SAMPLE SIZE CONSIDERATIONS

To identify the adequate sample size for the CARDIOCARE prospective study, a power analysis was performed with 2-tailed alpha = 0.05 and 1 - beta = 0.80. Based on that, and considering the 21% incidence of cardiotoxicity in our target population and the expected 10% drop-out rate, it was estimated that a total of 736 patients (that is, 368 patients in the intervention arm and 368 patients in the control arm) would be large enough to detect a 40% relative risk reduction in the incidence of increased levels of troponin I (taken as a cardiotoxicity proxy) in this population. Such a sample size would also allow the evaluation of the effectiveness of the behavioural and psychological interventions integrated into the study in mitigating, preventing, or delaying the onset of cardiotoxicity associated with oncological therapies for elderly breast cancer patients.
The sample size calculation was followed by Fisher's exact test, performed using G*Power software version 3.1.9.4. Considering our power analysis results and the number of patients affected by breast cancer each year, all clinical centres in the CARDIOCARE consortium agreed on the final recruitment goal of 750 patients (375 for the intervention arm and 375 for the control one).

DATA COLLECTION STORAGE AND SECURITY
A well-defined Data Management Plan has been submitted, providing detailed information on the procedures that will be implemented for data collection, storage, protection, retention, re-use and/or destruction, complying with the General Data Protection Regulation (GDPR).
By design, a robust data protection and security strategy will be implemented in all data collection and storage procedures in the CARDIOCARE platform. As part of the CARDIOCARE Data Management and High-Performance Computing (HPC), an electronic Case Report Form (eCRF) - accessible by all clinical partners - has been developed to serve as the data entry tool for all patient data. eCRF data will be uploaded and stored encrypted to the platform and systematically backed up in external RAID drives. An audit Log operation will be implemented to view the users' access history to the system, enabling the detection of any potential data

security breaches. After final quality checks at the end of the prospective study, the eCRF will be frozen and exported to the technical partners for statistical analysis performance.
All members of the CARDIOCARE consortium will take appropriate organisational and technical measures to prevent any event of abuse, accidental loss, destruction, or damage of collected data, enabling reinstate the system promptly if necessary.
Data quality, completeness and integrity will be ensured with visits by the Independent Data Monitoring Committee (IDMC) members, who will certify, in each clinical centre, the files' consistency, adherence to the study protocol and Good Clinical Practice guidelines, the accuracy of the eCRF forms, and the compliance with safety reporting. Investigators of each clinical centre will facilitate the IDMC members' jobs by cooperating and enabling direct access to all data sources to be verified.
Strict confidentiality of all personal and study-related data is ensured. All recruiting centres will sign an agreement document detailing their commitment towards complying with the relevant laws, regulations, codes of practice and obligations to publication.

ETHICS COMPLIANCE
All involved clinical centres submitted the new version (1.2) of the CARDIOCARE prospective study protocol to their Ethics Committees and got official approval.
This multicentric prospective study has been designed to comply with national (i.e., Good Clinical Practices) and international declarations (i.e., the Declaration of Helsinki) regulating proper ethical research involving human subjects, with Written Informed Consent which will be obtained from all participating patients. In particular, the study conduct is in line with the following regulations and norms:

- The Declaration of Helsinki, ethical principles for medical research involving human subjects, revised October 2013.
- The Convention for the Protection of Human Rights and Dignity of the Human Being concerning the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, Oviedo 1997.
- The Council for International Organizations of Medical Sciences, in collaboration with the World Health Organization, International Ethical Guidelines for Biomedical Research Involving Human Subjects, revised in 2016.
- The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research. Department of Health, Education, and Welfare (DHEW) publication (DHEW-05-78-0012), Washington, DC, 1978.

RESULTS

The active phase of the recruitment process began in May 2023 and preliminary results will be published in a scientific journal and made available for consultation on the CARDIOCARE project website. Data analysis and dissemination of the study results will be performed in 2024 and 2025.

DISCUSSION

The CARDIOCARE risk prediction model for cardiac toxicity will allow healthcare providers to identify and monitor trajectories across the field of cardiotoxicity and thus advise and intervene promptly on high-risk patients while saving resources on those presenting a low risk of developing cardiotoxicity. The model will be particularly tailored to detect the risk for cardiotoxicity in elderly breast cancer patients, that are at almost the same risk of cardiovascular disease as breast cancer relapse (Bardia et al. 2012; Park et al. 2017). Furthermore, even when not fatal, elderly breast cancer women are especially prone to develop cardiac morbidity as a collateral effect of oncological treatments (Zagar et al., 2016). Indeed, in this clinical population, cancer treatment cardiotoxic effects are often added to baseline age-related factors and pre-existing morbidity, leading to drug interaction complications resulting from polypharmacy (Chang et al., 2019; Mandelblatt et al., 2018), poorer health outcomes, and intrinsic capacity and QoL deterioration (Depboylu, 2020).

Considering the above, the CARDIOCARE mobile App, with its contents and health monitoring system, will provide elderly breast cancer women with the opportunity to learn how to best manage their multimorbidity while preserving and enhancing their physical and psychological intrinsic capacity as well as their overall QoL, including their relationship with others. They will also benefit from the continuous and home-based care that the mobile App allows by notifying them promptly when one or more health parameters are sub-optimal, clinician-developed suggestions on how to intervene to improve such parameters will follow right after.

In addition, the present study gives an opportunity to test the feasibility of digital tools (devices and mobile application) among this specific population of elderly patients (>=60) and identify the possible areas that need improvement so that, in the future, these types of digital tools and interventions can be successfully applied to the specific segment of patients considered here.

Healthcare providers will also vastly benefit from the health monitoring and technologically advanced tools employed for the current prospective study. Such devices, including the Mobile App, will provide clinicians with information on their patients' health, more integrated than the information they can obtain through standard Electronic Health Records (EHR) tools. The CARDIOCARE Mobile App and the wearable devices used for the study will, indeed, inform healthcare providers about several characteristics of their patients (psychological, behavioural, cognitive, and functional) which, based on the most updated scientific literature, are particularly relevant to determine the risk of elderly breast cancer patients of developing cardiac toxicity when exposed to oncological therapy (Bussotti and Sommalunga, 2018; Wang et al., 2023; Chan et al., 2023; Hill et al., 2023). Furthermore, by being informed on their patients' intrinsic capacity (physical and psychological) and other QoL-related aspects, healthcare providers can more easily and quickly identify each patient's care gaps and specific needs, and develop new and more integrated best practices, facilitating the implementation of personalised, patient-centred care.

The innovative CARDIOCARE model of care and its risk prediction model for cardiac toxicity hold promise from a socio-economic perspective as well. It is to be underlined that almost 40% of public spending in the healthcare sector concerns people over 60, with long-term care and hospital admissions being the primary cost drivers (Joling et al., 2018). Since healthcare

systems that successfully provide effective community-based care and services are likely to significantly optimise their public spending (Joling et al., 2018), healthcare institutions and insurance companies are seeking new ways to decrease treatment costs for chronic diseases such as cancer.

Moreover, previous research has highlighted considerably higher mortality rates among breast cancer patients with low socio-economic status (i.e., education, employment, income) compared to those whose socio-economic status is higher (Yu, 2009; Lundqvist et al., 2016). This is a critical datum, since socio-economic disadvantage may result in later-stage diagnosis and poorer access to and quality of care received. Using technologically advanced tools - provided to patients by the clinical centres - able to consistently monitor several health parameters beyond the time the patient stays at the clinical centre, the CARDIOCARE healthcare model attempts, on the one hand, to address the economic and societal challenges that afflict both our healthcare system finances and the patients in the lower socio-economic groups. Additionally, once the prospective study is concluded and the data analysed, a cost-effectiveness analysis will be performed, comparing the CARDIOCARE healthcare model to current practices.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report.

REFERENCES

1. Bardia, A., Arieas, E. T., Zhang, Z., DeFilippis, A., Tarpinian, K., Jeter, S., ... & Stearns, V. (2012). Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer. *Breast cancer research and treatment*, *131*, 907-914.
2. Booth, L. K., Redgrave, R. E., Folaranmi, O., Gill, J. H., & Richardson, G. D. (2022). Anthracycline-induced cardiotoxicity and senescence. *Frontiers in Aging*, *3*, 1058435.
3. Bussotti, M., & Sommaruga, M. (2018). Anxiety and depression in patients with pulmonary hypertension: impact and management challenges. *Vascular health and risk management*, 349-360.
4. Cardinale, D., Colombo, A., Sandri, M. T., Lamantia, G., Colombo, N., Civelli, M., Martinelli, G., Veglia, F., Fiorentini, C., & Cipolla, C. M. (2006). Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*, *114*(23), 2474–2481.

5. Carioli, G., Malvezzi, M., Rodriguez, T., Bertuccio, P., Negri, E., & La Vecchia, C. (2017). Trends and predictions to 2020 in breast cancer mortality in Europe. *The Breast*, *36*, 89-95.
6. Chan, H., Savoie, M. B., Munir, A., Moslehi, J., Anwar, M., Laffan, A., ... & Van Loon, K. (2023). Multi-Disciplinary Management in Rectal Cancer Survivorship: A Clinical Practice Review. *Journal of Gastrointestinal Cancer*, 1-14.
7. Chang, L., Weiner, L. S., Hartman, S. J., Horvath, S., Jeste, D., Mischel, P. S., & Kado, D. M. (2019). Breast cancer treatment and its effects on ageing. *Journal of Geriatric Oncology*, *10*(2), 346-355.
8. Chianca, M., Panichella, G., Fabiani, I., Giannoni, A., Aimo, A., Franco, A. D., ... & CARDINALE, D. (2022). Bidirectional relationship between Cancer and Heart Failure: insights on circulating biomarkers. *Frontiers in Cardiovascular Medicine*, 1739.
9. Denollet, J., Conraads, V. M., Brutsaert, D. L., De Clerck, L. S., Stevens, W. J., & Vrints, C. J. (2003). Cytokines and immune activation in systolic heart failure: the role of Type D personality. *Brain, behavior, and immunity*, *17*(4), 304-309.
10. Depboylu, B. (2020). Treatment and patient related quality of life issues in elderly and very elderly breast cancer patients. *Translational Cancer Research*, *9*(Suppl 1), S146.
11. Hill, L., Delgado, B., Lambrinou, E., Mannion, T., Harbinson, M., & McCune, C. (2023). Risk and management of patients with cancer and heart disease. *Cardiology and Therapy*, 1-15.
12. Joling KJ, et al. Quality indicators for community care for older people: A systematic review. PLoS ONE 2018;13(1):e0190298
13. Keramida, K., Farmakis, D., Bingcang, J., Sulemane, S., Sutherland, S., Bingcang, R. A., ... & Nihoyannopoulos, P. (2019). Longitudinal changes of right ventricular deformation mechanics during trastuzumab therapy in breast cancer patients. *European Journal of Heart Failure*, *21*(4), 529-535.
14. Lin, T. K., Lin, C. L., Li, Y. D., Huang, Y., Koo, M., & Weng, C. Y. (2020). Negative Affectivity Is Associated with a Higher Systolic and Diastolic Blood Pressure in Normotensive Middle-Aged and Older Adults: A Cross-Sectional Study. *Medicina* (Kaunas, Lithuania), 56(4), 160.
15. Lyon, A. R., Lopez-Fernandez, T., Couch, L. S., Asteggiano, R., Aznar, M. C., Bergler-Klein, J., ... & Van Der Pal, H. J. (2022). 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS) Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC). *European heart journal*, 43(41), 4229-4361.
16. Lundqvist, A., Andersson, E., Ahlberg, I., Nilbert, M., & Gerdtham, U. (2016). Socioeconomic inequalities in breast cancer incidence and mortality in Europe—a systematic review and meta-analysis. *The European Journal of Public Health*, *26*(5), 804-813.
17. Mandelblatt, J. S., Small, B. J., Luta, G., Hurria, A., Jim, H., McDonald, B. C., ... & Ahles, T. (2018). Cancer-related cognitive outcomes among older breast cancer survivors in the thinking and living with cancer study. *Journal of Clinical Oncology*, *36*(32), 3211.

18. Montazeri, K., Unitt, C., Foody, J. M., Harris, J. R., Partridge, A. H., & Moslehi, J. (2014). ABCDE steps to prevent heart disease in breast cancer survivors. *Circulation*, *130*(18), e157-e159.
19. Ng, C. G., Mohamed, S., Kaur, K., Sulaiman, A. H., Zainal, N. Z., Taib, N. A., & MyBCC Study group. (2017). Perceived distress and its association with depression and anxiety in breast cancer patients. *PloS one*, *12*(3), e0172975.
20. Park, N. J., Chang, Y., Bender, C., Conley, Y., Chlebowski, R. T., Van Londen, G. J., ... & Kuller, L. H. (2017). Cardiovascular disease and mortality after breast cancer in postmenopausal women: results from the Women's Health Initiative. *PloS one*, *12*(9), e0184174.
21. Pedersen, S. S., Von Känel, R., Tully, P. J., & Denollet, J. (2017). Psychosocial perspectives in cardiovascular disease. *European journal of preventive cardiology*, 24(3_suppl), 108-115.
22. Reddy, P., Shenoy, C., & Blaes, A. H. (2017). Cardio-oncology in the older adult. *Journal of Geriatric Oncology*, *8*(4), 308-314.
23. Rosengren, A., Hawken, S., Ôunpuu, S., Sliwa, K., Zubaid, M., Almahmeed, W. A., ... & Yusuf, S. (2004). Association of psychosocial risk factors with risk of acute myocardial infarction in 11 119 cases and 13 648 controls from 52 countries (the INTERHEART study): a case-control study. *The Lancet*, *364*(9438), 953-962.
24. Sawaya, H., Sebag, I. A., Plana, J. C., Januzzi, J. L., Ky, B., Cohen, V., ... & Scherrer-Crosbie, M. (2011). Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *The American Journal of Cardiology*, *107*(9), 1375-1380.
25. Singh, A., Kareem, H., Devasia, T., Khera, K., Chauhan, S., & Ganesh, P. (2018). Breast cancer and the heart: burden on the chest. *Journal of Cardiovascular Disease Research*, *9*(1).
26. Shubert, T. E., Goto, L. S., Smith, M. L., Jiang, L., Rudman, H., & Ory, M. G. (2017). The Otago Exercise Program: Innovative Delivery Models to Maximize Sustained Outcomes for High Risk, Homebound Older Adults. *Frontiers in public health*, 5, 54
27. Wang, Z., Fan, Z., Yang, L., Liu, L., Sheng, C., Song, F., ... & Chen, K. (2023). Higher risk of cardiovascular mortality than cancer mortality among long-term cancer survivors. *Frontiers in Cardiovascular Medicine*, *10*.
28. World Health Organization. (2006). A state of complete physical mental and social well-being and not merely the absence of disease or infirmity. *Constitution of the World Health Organization Basic Documents*, *45*, 1-20.
29. Yu XQ. Socioeconomic disparities in breast cancer survival: relation to stage at diagnosis, treatment and race. BMC Cancer 2009;9:364
30. Zagar, T. M., Cardinale, D. M., & Marks, L. B. (2016). Breast cancer therapy-associated cardiovascular disease. *Nature reviews Clinical oncology*, *13*(3), 172-184.

ABBREVIATIONS

CV: Cardiovascular
ICF: Informed Consent Form
BP: Blood Pressure
HR: Heart Rate
ECHO assessment: Echocardiographic assessment
ECG: Electrocardiogram
I/E checklist: Inclusion/Exclusion criteria checklist
AE: Adverse Event
BPN: Brain Natriuretic Peptide
CRP: C-Reactive Protein
CRS: Cardio Recording Session
HGS: Hand Grip Session
QoL: Quality of Life
Cardiac MRI: Cardiac Magnetic Resonance Imaging
miRNA: microRNA
SNP: Single Nucleotide Polymorphism
eCRF: electronic Case Report Form
HER2: Human Epidermal Growth Factor Receptor 2
EW = Expressive Writing
BPS = Best Possible Self
ABCDE: A = Activating event or situation; B = Beliefs; C = Consequences; D = Disputation of beliefs; E = Effective new approach
GSRS: Gastrointestinal Symptom Rating Score
ITT approach: Intention-to-treat approach
QALYs: Quality-Adjusted Life-Years
ICER: Incremental Cost-Effectiveness Ratio
GDPR: General Data Protection Regulation
HPC Platform: High-Performance Computing platform
IDMC: Independent Data Monitoring Committee
EHR: Electronic Health Records

APPENDIX

Table 2. Self-administered scales for each study time points

Psychological and behavioral assessment	May be one single or two visits		Day 0	Month 3	Month 6	Month 9	Month 12
	Day -15 T0	T1 (baseline)	Treatment start	T2	T3	T4	T5

Quality of life (EORTC-QLQ-30/ BR23)		✓		✓	✓	✓	✓
Fatigue FACIT-Fatigue		✓		✓	✓	✓	✓
Resilience (Brief Resilience Scale)		✓		✓			✓
Anxiety and Depression (PHQ4)		✓		✓	✓	✓	✓
Emotion Regulation Questionnaire (ERQI)		✓		✓			✓
Life Orientation Test Revised (LOT-R)		✓		✓			✓
Life Satisfaction (Single-item life satisfaction Measure)		✓	✓	✓	✓	✓	✓
Perceived social support (MSPSS)		✓		✓			✓
Self-control and self-management (SCMS)		✓		✓			✓
Cancer Behavior Inventory short form (CBI-B)		✓		✓	✓	✓	✓
Impact of Event Scale (IES-R)		✓		✓			✓
Perceived stress scale (PSS)		✓		✓	✓	✓	✓
Positive and Negative Affect (B-PANAS)		✓		✓			✓
Burden for Family Caregivers (BSFC-s). Optional.		✓		✓	✓	✓	✓
Nutritional questionnaire		✓		✓			✓