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STUDY DESIGN

Rationale and design of RESILIENCE: A prospective randomized clinical trial evaluating remote ischaemic conditioning for the prevention of anthracycline cardiotoxicity

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Aims There is a lack of therapies able to prevent anthracycline cardiotoxicity (AC). Remote ischaemic conditioning (RIC) has shown beneficial effects in preclinical models of AC.

Methods REmote iSchemic condItioning in Lymphoma PatIents REceiving ANthraCyclinEs (RESILIENCE) is a multinational, prospective, phase II, double-blind, sham-controlled, randomized clinical trial that evaluates the efficacy and safety of RIC in lymphoma patients receiving anthracyclines. Patients scheduled to undergo ≥5 chemotherapy cycles including anthracyclines and with ≥1 AC-associated risk factors will be randomized to weekly RIC or sham throughout the chemotherapy period. Patients will undergo three multiparametric cardiac magnetic resonance (CMR) studies, at baseline, after the third cycle (intermediate CMR), and 2 months after the end of chemotherapy. Thereafter, patients will be followed up for clinical events over an anticipated median of ≥24 months. The primary endpoint is the absolute change from baseline in CMR-based left ventricular ejection fraction (LVEF). The main secondary outcome is the incidence of AC events, defined as (1) a drop in CMR-based LVEF of ≥10 absolute points, or (2) a drop in CMR-based LVEF of ≥5 and <10 absolute points to a value <50%. Intermediate CMR will test the ability of T2 mapping to predict AC versus classical markers (left ventricular strain and cardiac injury biomarkers). A novel CMR sequence allowing ultrafast cine acquisition will be validated in this vulnerable population.

Conclusions The RESILIENCE trial will test RIC (a novel non-invasive intervention to prevent AC) in a cohort of high-risk patients. The trial will also test candidate markers for their capacity to predict AC and will validate a novel CMR sequence reducing acquisition time in a vulnerable population.

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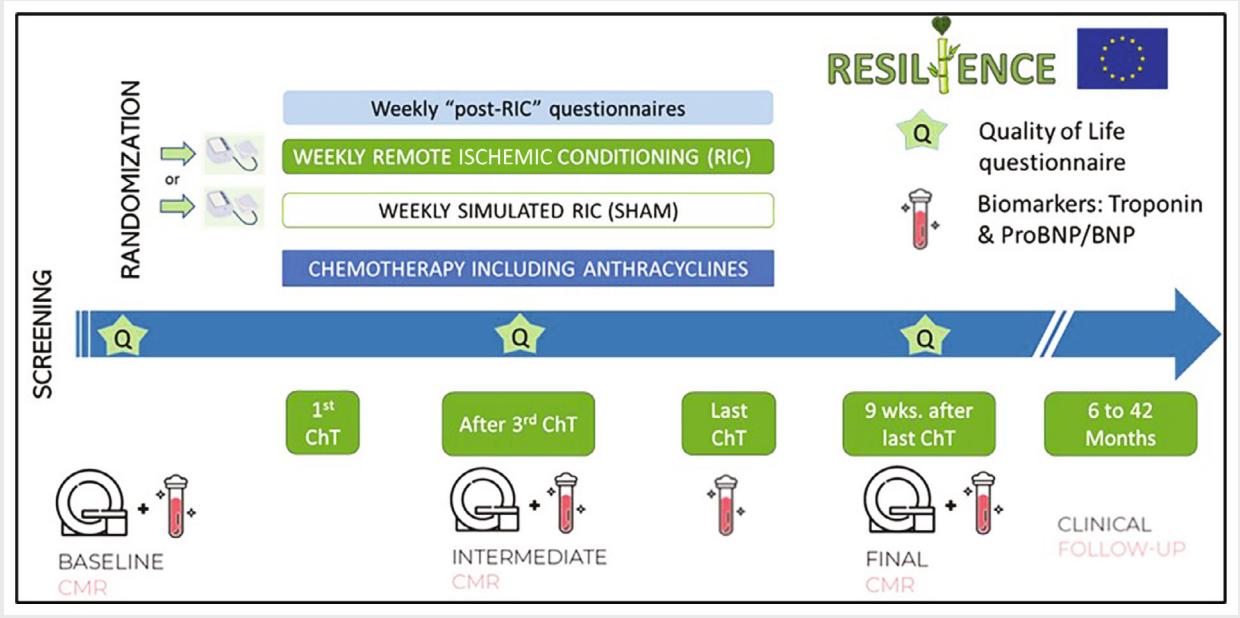
[†]Full list of investigators/collaborators is provided in online supplementary *Appendix S1*.

Graphical Abstract



RESILIENCE clinical trial overview. BNP, B-type natriuretic peptide; ChT, chemotherapy; CMR, cardiac magnetic resonance; Q, questionnaire; RIC, remote ischaemic conditioning.

Keywords Cardiotoxicity • Anthracyclines • Cardio-oncology • Cardioprotection • Heart failure • Ischaemic conditioning • Magnetic resonance imaging • Strain • Biomarkers • Randomized clinical trial

Introduction

Anthracyclines, alone or in combination, remain the first-line therapy for many cancers, including various forms of lymphoma, breast cancer, leukaemia, melanoma, and uterine and gastric cancers.[1] Every year, anthracyclines are administered to >3 million European citizens to treat a first cancer. The curative potential of anthracycline therapy is determined by appropriate dosing.[2] Anthracyclines have a well-known cardiotoxic effect that can result in irreversible injury to the myocardium, leading to chronic heart failure (HF).[3] While the major determinant of anthracycline cardiotoxicity (AC) is cumulative dose, the risk of this adverse effect is increased by older age and the presence of other comorbidities, including ischaemic cardiomyopathy, valvular heart disease, and hypertension.[4] An estimated >5% of cancer survivors live with chronic HF secondary to AC.[5] There is a pressing need to identify treatments able to prevent AC.[6]

Among several cardioprotective therapies that have been tested experimentally, a promising candidate for translation to the clinic is remote ischaemic conditioning (RIC). In RIC, brief episodes of ischaemia followed by reperfusion in one body part (usually a limb) render remote tissues and organs resistant to injury.[7] In pigs, which have a human-like cardiovascular anatomy, RIC has been shown to prevent AC through a mechanism involving mitochondrial protection.[8] RIC is a safe and effective, non-invasive, feasible, and inexpensive intervention that has mainly been tested in the context of myocardial infarction and stroke.[9,10]

Early identification of AC while patients are on-treatment is essential so that cardiovascular follow-up can be intensified, general HF therapy initiated, and cancer treatment regimens eventually modified. The currently recommended criterion for early AC diagnosis is echocardiographic global longitudinal strain (GLS).[4] However, GLS disturbances are not detected until after the appearance structural damage to the myocardium. An ideal early AC marker would be altered before the appearance of any structural or functional abnormality. In a large animal (pig) model, the earliest identification of AC was achieved with cardiac magnetic resonance (CMR) T2 mapping.[11] While T2 prolongation has yet to be formally validated as an AC marker in humans, pilot clinical data suggest that T2 mapping is altered early in cancer patients,[12] suggesting that CMR could be an ideal risk-stratification tool for cancer patients on anthracyclines. However, CMR acquisition times are

normally between 45 and 60 min.[13] Cancer patients are a vulnerable population, and long scan times can cause particular discomfort. A novel CMR methodology was recently developed that massively reduces scan times to less than 1 min,[14] but this new method has not previously been tested in a vulnerable patient population.

RESILIENCE (REmote iSchemic condItioning in Lymphoma PatIents REceiving ANthraCyclinEs) is a European Commission-funded project aimed at reducing the prevalence of anthracycline chemotherapy-related HF in cancer survivors. The central activity is a randomized clinical trial evaluating the efficacy and safety of RIC in lymphoma patients receiving anthracyclines and at risk of cardiotoxicity (RESILIENCE trial, NCT05223413). The project additionally includes prospective controlled studies to validate T2 mapping as an early marker of AC and ultrafast CMR to achieve massively reduced scan times.

Methods

Study design

RESILIENCE is a multinational, phase II, prospective, double-blind (sham-controlled) randomized clinical trial evaluating the efficacy and safety of RIC in lymphoma patients receiving anthracyclines and at risk of cardiotoxicity. The sponsor is the Centro Nacional de Investigaciones Cardiovasculares (CNIC), a publicly funded non-profit research institute in Madrid, Spain. The study is funded by the European Commission through the Horizon 2020 Framework Programme, call H2020-SC1-BHC-2018-2020 'Better Health and care, economic growth and sustainable health systems'.

The enrolled study population consists of patients with a first lymphoma diagnosis, scheduled to undergo ≥5 chemotherapy cycles including anthracyclines, and having a risk factor for AC ≥1. Eligible patients undergo a baseline CMR study and will be randomized to RIC or a sham procedure, with stratification by gender, recruitment centre, and baseline left ventricular ejection fraction (LVEF) (41–50%, 51–60%, >60%). Patients undergo three CMR studies: before starting anthracycline-based chemotherapy (baseline), between the third and fourth chemotherapy cycles, and 9 weeks after the final chemotherapy cycle. On the same day as the CMR studies, blood samples are obtained for the determination of cardiac injury biomarkers (high-sensitivity troponin [hsTn] and B-type natriuretic peptide [BNP]). Patients are monitored for clinical events at 6, 12, 18, 30, and 42 months after enrolment. When the last patient to be enrolled undergoes the final CMR, clinical follow-up will be closed for all patients, and patients who have not reached the 42-month follow-up will attend a final visit at that time. The anticipated median clinical follow-up is therefore 24 months. The trial outline is depicted in the *Graphical Abstract*.

Study hypothesis

The main hypothesis of the RESILIENCE trial is that RIC will reduce the incidence of AC. A second hypothesis is that T2 relaxation time in the intermediate CMR exam will predict AC more accurately than other markers (left ventricular [LV] strain or circulating biomarkers). The third hypothesis is that in this vulnerable population of cancer patients, the ultrafast ESSOS three-dimensional (3D) single breath-hold CMR cine sequence will yield similar results to the standard two-dimensional (2D) sequence.

Study population: inclusion/exclusion criteria

Eligible patients are those with a first diagnosis of lymphoma (non-Hodgkin or Hodgkin) scheduled to undergo ≥5 chemotherapy cycles containing anthracyclines and having at least one risk factor for AC. Patients fulfilling all inclusion and no exclusion criteria on screening undergo baseline CMR. When CMR-based LVEF is confirmed to be above 40%, patients are randomized 1:1 to RIC versus simulated RIC (sham). Inclusion and exclusion criteria are listed in *Table 1*.

Randomization

Baseline CMR data are transferred to the core lab, where LVEF is quantified within two working days. CMR-based LVEF qualification includes its categorization as 41–50%, 51–60%, and >60% for stratification purposes. Further CMR analyses are performed later (see CMR section). Local investigators (blinded to core lab LVEF quantification) are then informed that the patient can be randomized and access the web-based electronic case report form (eCRF)-management application REDCap and click for randomization. Randomization is stratified by LVEF (41–50%, 51–60%, and >60%), sex (male/female), and enrolling centre. The system assigns a randomization number that serves as a unique device identifier. The assigned device corresponds to RIC or the sham procedure (double-blind allocation). See RIC device section for additional information.

Remote ischaemic conditioning

Sham devices

Remote ischaemic conditioning has been tested in several large randomized clinical trials of several thousands of patients experiencing a myocardial infarction[10] or stroke[15] or undergoing cardiac surgery,[16,17] proving to be extremely safe. For this trial, devices were purchased from Seagull Aps (one device per enrolled patient). Seagull Aps RIC devices were used in a recent trial enrolling 1500 stroke patients, with no reported serious device-related safety concerns.[15]

The device has two independent components: a portable blood pressure monitor, and a CE-marked blood pressure cuff. A device of the type to be used in the RESILIENCE trial is shown in *Figure 1*. The pressure-monitor software has been modified to automatically apply a complete RIC or sham session (four cycles of 5 min inflation and 5 min deflation) instead of a regular blood pressure measurement. The RIC and sham procedures are distinguished by the cuff inflation pressure used: above systolic blood pressure in the RIC procedure, to induce arm ischaemia; or residual pressure (≈20 mmHg) in the sham procedure. When switched on, the device automatically takes a regular blood pressure reading and then initiates the RIC or sham procedure. The device automatically shuts down after completing the fourth RIC/sham cycle.

The device records full information related to each use (including cycles, inflation pressures, etc.), and the aggregated information for multiple intervention days is later downloaded by the research team during the next site visit. In this way, device operation will allow the assessment of adherence to intervention.

Sham intervention protocol

Upon enrolment, patients receive training in how to operate the RIC/sham device. The first RIC/sham intervention is performed and

Table 1 Inclusion/exclusion criteria

Inclusion criteria	Exclusion criteria
1. Signed informed consent form	1. Previous treatment with anthracyclines
2. ≥18 years old	2. Previous clinical diagnosis of heart failure
3. First NHL or HL diagnosis	3. Permanent atrial fibrillation
4. Scheduled to undergo ≥5 chemotherapy cycles including any anthracycline	4. Severe valvular or sub-valvular heart disease
5. Pre-chemotherapy LVEF >40%	5. Severe peripheral arterial disease in the upper extremities or arteriovenous shunt
6. Sinus rhythm on screening ECG	6. Diabetic neuropathy
7. Presence of ≥1 of the following risk factors for AC:	7. Diabetes actively treated with sulfonylureas
Previous coronary artery disease[a]	8. Contraindication for contrast-enhanced CMR[b]
LVEF 41–54% on screening echocardiography	9. Platelet count <50 000/μl in any blood test in the previous 3 months
Age ≥65 years old	10. Participation in other clinical trials
Previous diagnosis of arterial hypertension	11. Inability to consent or undergo study follow-up
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	
Current smoker (≥20 packs of cigarettes per year)	
Former smoker (≥20 packs of cigarettes per year) who quit ≤10 years before	
BMI ≥30 kg/m^2	
LV thickness ≥12 mm on echocardiography screening	
High alcohol intake (≥21 standard drinks per week)	
Previous diagnosis of diabetes	
Previous non-anthracycline-based chemotherapy	

AC, anthracycline cardiotoxicity; BMI, body mass index; CMR, cardiac magnetic resonance; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HL, Hodgkin lymphoma; LV, left ventricular; LVEF, left ventricular ejection fraction, NHL, non-Hodgkin lymphoma.

[a]Any of the following: (i) previous coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting); (ii) medical history of significant non-revascularized coronary stenosis; (iii) previous acute coronary syndrome/acute myocardial infarction with LVEF >40%.

[b]Any of the following: (i) severe claustrophobia; (ii) any device which is known to threaten or pose a hazard in any magnetic resonance environment; (iii) presence of a pacemaker, implantable cardioverter-defibrillator, or cardiac resynchronization device.

Figure 1 Remote ischaemic conditioning device. The remote ischaemic conditioning device is very similar to a blood pressure monitor, but with modification to maintain a target pressure of 200 mmHg for 5 min, causing ischaemia in the upper limb. In remote ischaemic conditioning, brief, reversible episodes of ischaemia followed by reperfusion in one body part (usually an arm) render remote tissues and organs resistant to injury.

completed under the supervision of study nurses before the initiation of chemotherapy, on the same day as the first anthracycline injection. Patients then take the device home and perform the intervention themselves once a week throughout the chemotherapy period. In addition to the weekly at-home RIC/sham intervention, patients undergo daily RIC/sham procedures during each chemotherapy cycle, with the intervention completed before commencing anthracycline infusion. The final RIC/sham intervention is scheduled for 1 week after the final chemotherapy cycle.

Study endpoints

Primary endpoint:

- Absolute change in LVEF (between baseline and either follow-up CMR, whichever shows the lower LVEF).

Key secondary endpoints:

- Rate of AC events (based on the drop in LVEF between baseline and either of follow-up CMR, whichever shows the lower LVEF). An AC event is defined as either of the following: (i) a drop in LVEF ≥10 absolute points regardless of the absolute value of the follow-up LVEF; (ii) a drop in LVEF ≥5 and <10 absolute points to a follow-up LVEF <50%.
- Rate of atrial fibrillation.
- Rate of hospital admission for sustained ventricular tachycardia or ventricular fibrillation or resuscitated cardiac arrest.
- Time to all-cause death.
- Time to hospitalization for HF.
- Tumor regression.
- Change in quality of life (QoL, scored by questionnaire) between baseline and two time points, coinciding with the intermediate CMR (after the third chemotherapy cycle) and the final CMR (9 weeks after the final chemotherapy cycle).

Exploratory endpoints:

- Sex differences in the incidence of the primary endpoint.
- Sex differences in the incidence of AC events.
- Difference between study groups (RIC vs. sham) in the change in myocardial perfusion between CMR scans.
- Difference between study groups in the change in T1 and T2 relaxation times between CMR scans.
- Differences between study groups in changes in LV strain derived from tagging, feature tracking, and fast-SENC sequences between CMR scans
- Differences between study groups in late gadolinium enhancement (LGE) area and extracellular volume fraction in the final CMR.
- Differences between study groups in the change in end-diastolic volume between CMR scans.

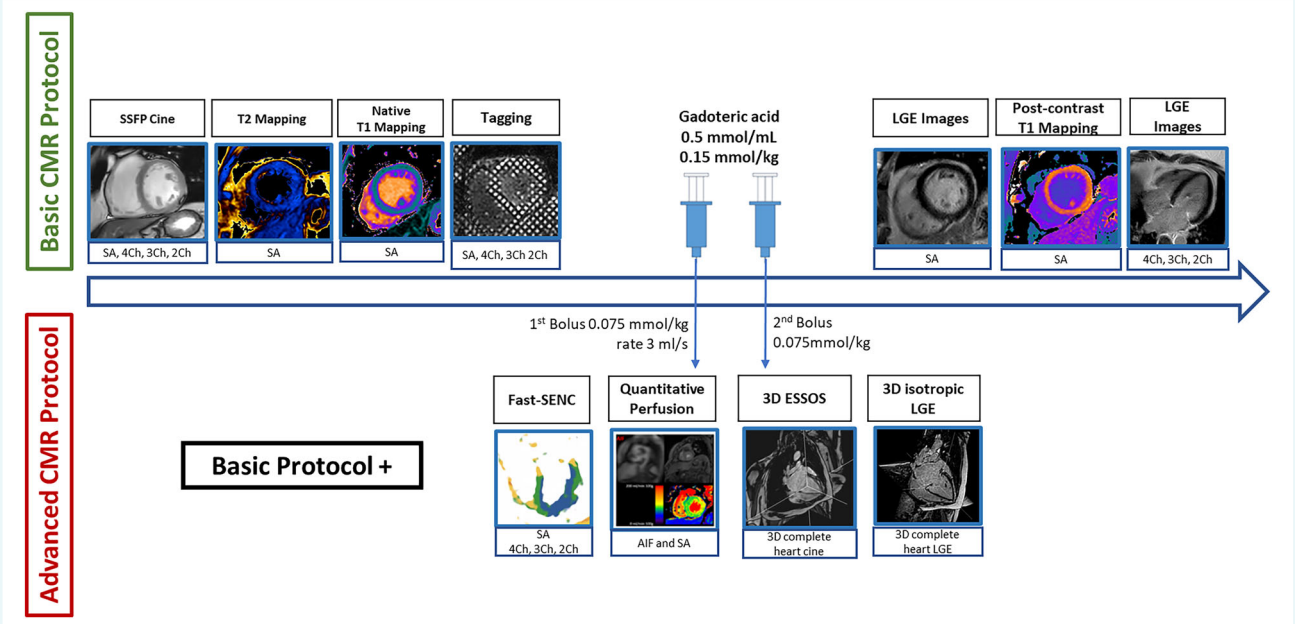


Figure 2 RESILIENCE cardiac magnetic resonance (CMR) imaging protocols. The CMR protocols include steady state free precession (SSFP) cine imaging in long-axis orientation (2-, 3-, and 4-chamber [Ch]) and short-axis orientation (SA). All patients undergo the basic protocol, and a predicted >50% of patients will additionally undergo the advanced protocol. Each patient will undergo the same procedure (basic or basic + advanced) in all three CMR studies (baseline, intermediate, and final 9 weeks after last chemotherapy cycle). The basic CMR protocol includes assessment of two-dimensional cardiac anatomy and function, left ventricular strain tagging, T2 mapping, pre- and post-gadolinium T1 mapping, and T1W late gadolinium enhancement (LGE). The advanced CMR protocol includes the following sequences: fast-strain encoded (fast-SENC), quantitative perfusion imaging, ultrafast (single breath-hold) ESSOS (enhanced sensitivity encoding [SENSE] by static outer volume subtraction) three-dimensional (3D) cine sequence, and ultrafast 3D isotropic LGE.

- Difference between study groups in the change in LV sphericity index between CMR scans.
- Difference between study groups in the change in CMR-measured LV diastolic function between CMR scans.

Quality of life evaluation

Quality of life is assessed using three widely used questionnaires for this vulnerable population: the Hematological Malignancy Specific Patient-Reported Outcome Measure (HM-PRO), the EuroQoL EQ-5D Questionnaire, and the Kansas City Cardiomyopathy Questionnaire (KCCQ-12).

In addition to these three validated QoL questionnaires, an 11-item ad hoc questionnaire to evaluate discomfort produced by the intervention is completed 90 min after each RIC/sham session. The first nine questions on this ad hoc questionnaire ask about the perception of any of the following signs and symptoms affecting the cuffed arm: pain (scored from 0 to 10); tingling, such as pins and needles; numbness; tightness; redness or bluish marbling; skin marking where the cuff was placed; swelling of the fingers or hand; loss of sensitivity in the arm, forearm, or fingers; and the presence of haematoma. Questions 2 through 8 have three response options: *No/A little/A lot*, whereas question 9 has four: *None/Petechiae (tiny purple, red, or brown spots on the skin)/Mild haematoma/ Large haematoma*. Item 10 asks patients to describe (in free text) any other sign or symptom not found on the list, thus providing space for the reporting of less likely symptoms such as difficulty in moving the arm, hand, or wrist. The final item asks if the device functions correctly and has four response options: *Yes/It does not work/It does not perform or complete the four cycles/It does not inflate and/or deflate*.

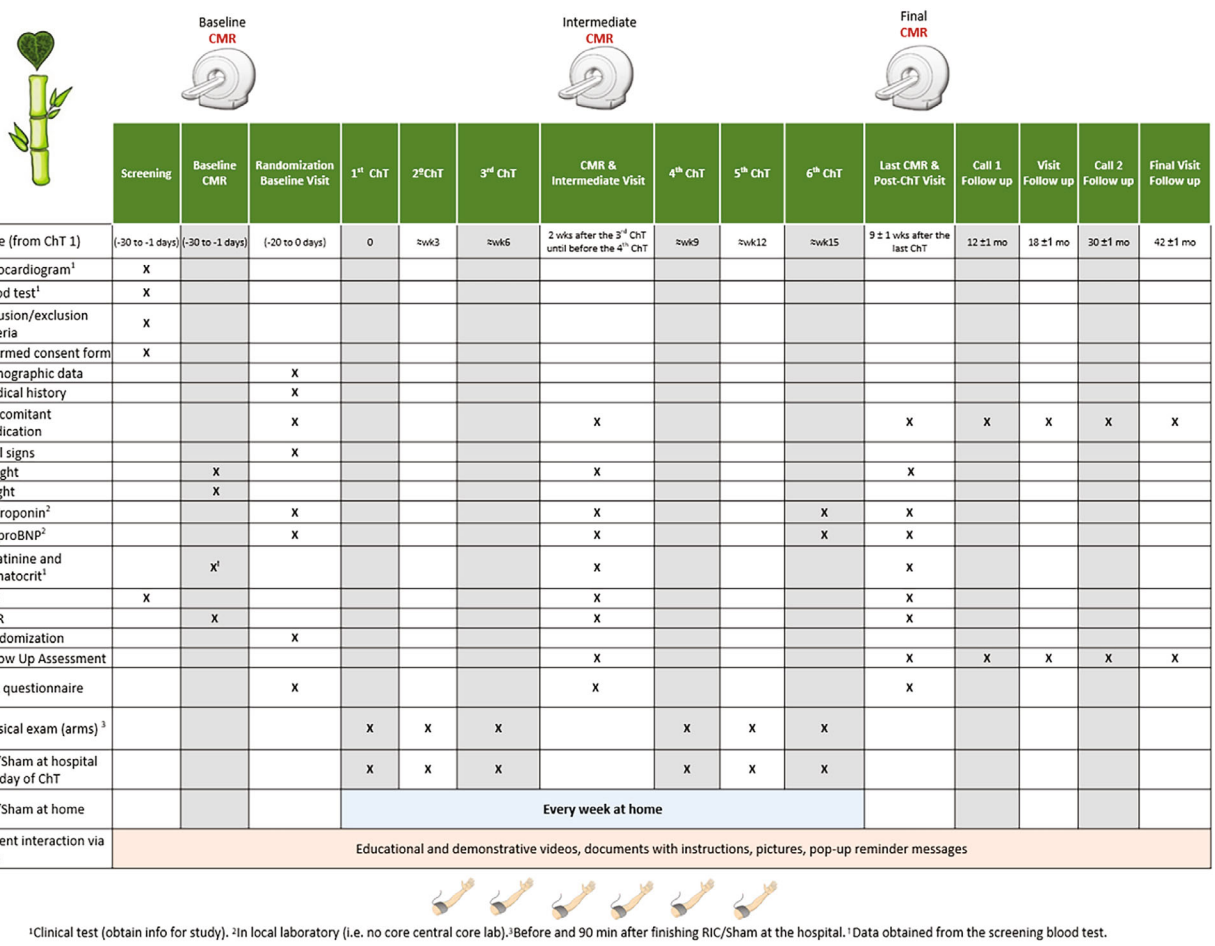
Cardiac magnetic resonance acquisition protocol and analysis

Overt AC, the main outcome measure in RESILIENCE, will be identified with CMR. The CMR scans will also be used to validate two novel CMR methodologies: T2 mapping for the early diagnosis of cardiotoxicity, and the ESSOS sequence for massively reduced scan time.

The main parameter used for the diagnosis of overt AC is LVEF deterioration.[18] CMR is the most accurate technique for determining LVEF, showing the least variability of all imaging modalities. Furthermore, CMR is the gold-standard methodology for cardiac anatomical and functional evaluations. In line with international consensus documents,[13] the primary and most key secondary outcome measures in RESILIENCE are CMR based.

Imaging protocol

All patients will undergo a comprehensive basic protocol that includes 2D assessment of cardiac anatomy and function, LV strain tagging, T2 mapping, pre- and post-gadolinium T1 mapping, and T1w LGE. In addition, >60% of patients (those enrolled at centres equipped with specific Philips magnets) will undergo an additional advanced protocol comprising ultrafast (single breath-hold) ESSOS 3D cine sequence,[14] ultrafast



	Screening	Baseline CMR	Randomization Baseline Visit	1st ChT	2ºChT	3rd ChT	CMR & Intermediate Visit	4th ChT	5th ChT	6th ChT	Last CMR & Post-ChT Visit	Call 1 Follow up	Visit Follow up	Call 2 Follow up	Final Visit Follow up
Time (from ChT 1)	(-30 to -1 days)	(-30 to -1 days)	(-20 to 0 days)	0	≈wk3	≈wk6	2 wks after the 3rd ChT until before the 4th ChT	≈wk9	≈wk12	≈wk15	9 ± 1 wks after the last ChT	12 ±1 mo	18 ±1 mo	30 ±1 mo	42 ±1 mo
Echocardiogram[1]	X														
Blood test[1]	X														
Inclusion/exclusion criteria	X														
Informed consent form	X														
Demographic data			X												
Medical history			X												
Concomitant medication			X				X				X	X	X	X	X
Vital signs			X												
Weight		X					X				X				
Height		X													
hs Troponin[2]			X				X			X	X				
NT-proBNP[2]			X				X			X	X				
Creatinine and Hematocrit[1]		X[1]					X				X				
ECG	X						X				X				
CMR		X					X				X				
Randomization			X												
Follow Up Assessment							X				X	X	X	X	X
QoL questionnaire			X				X				X				
Physical exam (arms) [3]				X	X	X		X	X	X					
RIC/Sham at hospital the day of ChT				X	X	X		X	X	X					
RIC/Sham at home				Every week at home											
Patient interaction via App	Educational and demonstrative videos, documents with instructions, pictures, pop-up reminder messages														

[1]Clinical test (obtain info for study). [2]In local laboratory (i.e. no core central core lab).[3]Before and 90 min after finishing RIC/Sham at the hospital. [1] Data obtained from the screening blood test.

Figure 3 Activity flow-chart. ChT, chemotherapy cycle; CMR, cardiac magnetic resonance; ECG, electrocardiogram; hs, high-sensitivity; NT-proBNP, N-terminal pro-B-type natriuretic peptide; QoL, quality of life.

(single breath-hold) 3D isotropic LGE,[14] quantitative perfusion imaging,[19] and fast-SENC.[20] The CMR protocol is summarized in *Figure 2*.

Cardiac magnetic resonance analysis

All scan data are transferred to the core imaging laboratory at the CNIC for blinded analysis. All analyses are performed by technicians specialized in cardiac imaging and reviewed by two cardiologists specialized in advanced cardiac imaging. Data from analyses are uploaded to the corresponding eCRF. Within two working days of the baseline CMR scan, baseline LVEF is analysed and uploaded to the eCRF for stratified randomization. All other analyses are performed later. Studies are analysed in a random order.

Cardiac anatomy, function, T1/T2 mapping, LGE, quantitative perfusion and ESSOS are analysed with the Philips Intellispace Portal application. LV strain determined by tagging and feature tracking is analysed with the commercially available Segment application (http://segment.heiberg.se), and LV strain determined by fast-SENC is analysed with the Myostrain application, providing global and segmental longitudinal and circumferential strain.

Before opening for recruitment, all enrolling centres underwent a quality control screen consisting of a complete CMR study obtained with precise adherence to the trial protocol. These tests have been reviewed to ensure sufficient quality for satisfactory quantification of all study parameters.

Follow-up and study outcomes

In addition to follow-up sessions coinciding with attendance for CMR scans and chemotherapy, a further four follow-up sessions are scheduled, at 12, 18, 30, and 42 months after recruitment. The first and third of these are telephone sessions, whereas the second and final sessions are in-person. When the last enrolled patient reaches the final CMR, this will mark the end of the study follow-up period, and all actively participating patients will be scheduled to attend the hospital for the final follow-up session, regardless of when the previous visit was. The anticipated median follow-up is thus 24 months (minimum 6 months, maximum 42 months). The study activities are summarized in *Figure 3*.

RESILIENCE has an expected duration of 5 years from the trial launch in 2021. A minimum follow-up of all patients will be performed 9 weeks after the last chemotherapy cycle (approximately 6 months after recruitment).

Sample size calculation

At 9 weeks after the final chemotherapy cycle (coinciding with the final CMR), we anticipate an absolute change in LVEF (primary endpoint)

of five points in the sham group. A total of 506 patients (253 per group) with baseline and follow-up CMR will be needed to detect a 40% relative reduction in the intervention group (a 3% drop in LVEF in absolute terms), with a common standard deviation of 8.8 points, 80% power, and two-sided alpha = 0.05. Based on a predicted maximum withdrawal from follow-up CMR of 17% (102 patients), the target sample size is set at 608 patients (304 per group).

As of 31 January 2024, patient enrolment had begun at all 18 centres, located in six countries (online supplementary *Appendix S1*), and 148 patients had been enrolled. Up-to-date real time information can be found in the newsletters posted on the project webpage (https://resilience-h2020.com/).

RESILIENCE consortium, participating centres

The RESILIENCE project receives funding from the European Union Horizon 2020 Research and Innovation Programme under grant agreement No. 945118; RESILIENCE. The project coordinator is the CNIC in Madrid, Spain. Other partners are the European Society of Cardiology (ESC), France; IIS-Fundación Jiménez Díaz, Spain; Philips Healthcare, The Netherlands; Academisch Medisch Centrum Bij De Universiteit Van Amsterdam, The Netherlands; Aarhus Universitetshospital, Denmark; Instituto Portugues de Oncologia de Lisboa Francisco Gentil EPE, Portugal; GLSMED Learning Health SA-Hospital da Luz, Portugal; Heinrich-Heine-Universität Düsseldorf, Germany; Centre Regional de Lutte Contre le Cancer Henri Becquerel Rouen, France; Centro de Investigacion Biomedica En Red (CIBER), Spain; and Philips Iberica, Spain. Other centres participate as third parties for trial execution and are listed in online supplementary *Appendix S1*.

Lymphoma Coalition Europe (LCE) collaborates with the project.

Discussion

The introduction of anthracyclines, incorporated into various immunochemotherapy regimens, was a significant breakthrough in the prognosis of patients with cancer. Unfortunately, however, cancer survivors often develop AC, limiting their QoL. A third of patients receiving high-dose anthracyclines develop some degree of AC, and irreversible injury leading to chronic HF[4] occurs in a smaller proportion (approximately 6% of cancer survivors).[5] Given the large numbers of patients receiving anthracyclines every year in Europe, these proportions translate into a vast population of cancer survivors living with AC (an estimated >1 million EU citizens). This problem is expected to intensify as a consequence of increasing cancer incidence and survival rates. For cancer survivors, the trade-off between cancer and chronic HF is an enormous psychological burden, and the growing incidence of chronic HF also has devastating consequences for healthcare systems.

Randomized clinical trials testing diverse cardioprotective AC prevention strategies have produced contrasting results. One of the most attractive pharmacological strategies is to encapsulate anthracyclines in pegylated or non-pegylated liposomes; however, this approach is not approved for AC prevention in Europe.[21,22] Another pharmacological strategy involves the use of dexrazoxane, an iron chelator that blocks the formation of anthracycline–iron complexes and thus decreases superoxide radical generation. Dexrazoxane also induces changes in the conformation of topoisomerase 2b. However, dexrazoxane does not show a consistent cardioprotective effect against AC, and there has been no definitive trial.[23]

Several, mostly small, trials have tested the AC-protective potential of drugs widely used in cardiovascular medicine. Among the most frequently tested therapies are beta-blockers,[24–26] renin–angiotensin–aldosterone system inhibitors,[27–29] and statins,[30–34] albeit results are not conclusive. In RESILIENCE, randomization is stratified for baseline LVEF, sex and enrolling centre. We decided not to stratify for established cardiovascular therapies with possible cardioprotective effects due to the intermediate size of the trial. Still, all baseline (and follow-up) medications will be collected and we will be able to account for their use.

The most encouraging results so far have come from the STOP-CA trial,[34] which compared the cardioprotective effect of 40 mg/day atorvastatin versus placebo in 300 lymphoma patients receiving moderate-to-high dose anthracyclines. The incidence of cardiotoxic events (a pre-specified decline in LV systolic function on CMR) was significantly lower in patients allocated to the statin treatment arm. In contrast, another recent (smaller) CMR-based trial in patients with diverse cancers found no cardioprotective effect of 40 mg/day atorvastatin.[33] Like the RESILIENCE trial, the STOP-CA trial[34] enrolled patients with lymphoma who were scheduled for moderate-to-high dose anthracycline chemotherapy (and thus had an elevated risk for AC) and used CMR as the main outcome measure. The RESILIENCE population is expected to have an even higher AC risk because aside from moderate-to-high anthracycline dose participants must have ≥1 additional AC risk factor (see inclusion criteria in *Table 1*). Risk factors that predispose patients to AC include a history of ischaemic heart disease, previous exposure to anticancer treatments, and hypertension. The selected risk factors in RESILIENCE are aligned with the latest ESC cardio-oncology guidelines (detailed information on AC risk factors is presented in Table 4 of these guidelines).[4] One possible reason why most previous trials of AC prevention strategies have failed is that they enrolled all comers rather than focusing on patients with risk factors for this adverse event.[35] The anticipated risk-factor profile in RESILIENCE predicts a very high risk for AC in this population, thus maximizing the potential benefits of an effective cardioprotective intervention. Despite elevated cardiac biomarkers at baseline is considered a moderate risk factor for AC,[4] we decided not to include this among our criteria. Two main reasons drove us to this decision: (i) elevated BNP has been proposed to be associated with cancer-related inflammatory status and not necessarily with a cardiac condition[36,37]; and (ii) for the specific case of lymphoma, N-terminal proBNP has been shown to be a cancer-related prognostic marker.[38] For the same reasons, cardiac biomarker dynamics between groups are not among the pre-specified endpoints. However, the same day of each CMR study, cardiac injury biomarkers (hsTn) and BNP will be obtained per protocol for further post-hoc analyses.

The cardioprotective intervention to be tested in the RESILIENCE trial is RIC. The selection of this treatment is based on consistent pre-clinical experimental results.[8] In a pig

model of AC that results in severe LV systolic dysfunction after five cycles of doxorubicin (every second week), the application of RIC before each doxorubicin dose resulted in significant LVEF preservation.[8] In the same pre-clinical trial, transmission electron microscopy indicated that RIC protects against AC by preserving mitochondrial structure and function,[8] a suitable mechanism of action given the central role of mitochondrial damage in AC.[39] Another possible benefit of this mechanism of action of RIC is that it differs from that of other potential cardioprotective strategies such as statins, and is thus likely to be non-redundant with those approaches.[34]

The effects of RIC in preventing AC have been reported in two very recent small clinical trials.[40,41] In the ERIC-ONC trial,[40] 55 adult patients (mean age 49 years) receiving anthracyclines were randomly assigned to either RIC or sham before each chemotherapy cycle. The primary outcome, circulating levels of cardiac troponin (cTn), did not differ between groups. The trial was underpowered and prematurely halted due to the COVID-19 pandemic. Notably, at 3 months, there were minimal changes in echocardiography-determined LVEF and LV GLS in either group, suggesting that the population had a very low AC risk. The second trial investigated the effects of RIC in a paediatric population of 68 patients (mean age 11 years) with diverse cancers.[41] The primary outcome was again circulating cTn and again did not differ between groups. In this trial, the mean cumulative anthracycline dose was low, reflecting the low AC risk of this population. AC prevalence was very low in both trials, and neither trial showed evidence of deteriorated LV function, indicating that anthracyclines did not induce significant cardiomyopathy in these populations and thus limiting the ability of these trials to demonstrate a cardioprotective effect of any intervention. Unlike these trials, the RESILIENCE population will have a high AC risk, increasing the chance of documenting a protective effect of RIC in a more vulnerable population. Another important difference is that the primary outcome in RESILIENCE is directly assessed myocardial function and composition by CMR, not circulating cTn. The release of cTn to the bloodstream is in most instances secondary to the destruction of cardiomyocytes, and thus does not inform on the frequent association of AC with dysfunctional but viable cardiomyocytes. These dysfunctional cardiomyocytes result in functional ventricular deterioration, but not necessarily in significant troponin release to the bloodstream.

One of the key secondary outcomes in RESILIENCE is the incidence of AC events, pre-defined as a binary outcome according to the drop in LVEF. A similar approach was taken in the STOP-CA trial, in which the incidence of AC events was the primary outcome (pre-defined as an absolute decline in LVEF $\geq$10% from pre- to post-chemotherapy to a final value of <55%).[34] The AC event criteria in RESILIENCE differ slightly from those in STOP-CA, with an AC event defined as either an absolute drop in LVEF of 10% regardless of the final value or an absolute drop of 5–10% to an LVEF <50%. Establishing endpoints based on cardiac function thresholds and dichotomizing patients into categories of absence or presence of cardiotoxicity aligns with the stratification of AC proposed by the ESC cardio-oncology clinical practice guidelines.[4]

Cardiac magnetic resonance is established as the best modality for the evaluation of cardiac anatomy, function, and tissue composition in a single session. CMR can also be used to evaluate the status of the microcirculation, another compartment affected by AC.[42] CMR is therefore recommended in consensus documents as the main outcome measure for phase 2 trials.[13,43] In the RESILIENCE trial, 608 patients at high-risk for AC will undergo three serial scans with a comprehensive state-of-the-art CMR protocol over a 6-month period. The selected CMR time points are based on previous AC studies. Most incidences of anthracycline chemotherapy-related cardiotoxicity manifest within the first year.[44]

The CMR protocol in RESILIENCE includes evaluation of anatomy and function, tissue characterization, LV strain, and analysis of extracellular space (*Figure 2*). This large-scale evaluation in a controlled randomized trial, including >1500 CMR scans, represents a pioneering effort to comprehensively assess cancer patients undergoing chemotherapy. RESILIENCE will provide robust scientific evidence supporting the utility of CMR for the management of patients with cancer and at high-risk for AC, contributing to the implementation of personalized approaches. A large subgroup of the RESILIENCE participants will additionally be examined using new CMR sequences not yet available in daily practice: the ESSOS 3D single breath-hold cine imaging sequence,[14] quantitative perfusion,[19] and fast-SENC.[20,45]

The European Commission-funded RESILIENCE trial is a patient-centred endeavour that will contribute to improved care of cancer patients at risk for AC. The trial has been designed to address several key challenges within a single population of ~600 study participants: testing the utility of RIC as an innovative cardioprotective intervention, improving early AC diagnostic algorithms, and validating novel CMR sequences aimed at improving the comfort of these vulnerable patients. By using a highly comprehensive CMR protocol, RESILIENCE will not only employ the most accurate method for determining the primary endpoint, but also enable comparison of T2 relaxation time prolongation, LV strain, and cardiac injury markers as early markers of AC. The programmed testing of the ultrafast CMR cine sequence moreover has the potential to establish a new gold standard for the rapid assessment of cardiac anatomy and function in a single breath-hold CMR exam, an advance that would increase accessibility of this modality to vulnerable populations, such as elderly, paediatric, and cancer patients.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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