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Protocol update and preliminary results of EACVI/HFA Cardiac Oncology Toxicity (COT) Registry of the European Society of Cardiology

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Abstract

Aims European Association of Cardiovascular Imaging/Heart Failure Association Cardiac Oncology Toxicity Registry was launched in October 2014 as a European Society of Cardiology multicentre registry of breast cancer patients referred to imaging laboratories for routine surveillance, suspected, or confirmed anticancer drug-related cardiotoxicity (ADRC). After a pilot phase (1 year recruitment and 1 year follow-up), some changes have been made to the protocol (version 1.0) and electronic case report form.

Methods and results Main changes of the version 2.0 concerned exclusion criteria, registry duration, and clarification of the population characteristics. Breast cancer radiotherapy has been removed as an exclusion criterion, which involves now only history of a pre-chemotherapy left ventricular dysfunction. The period for long-term registry recruitment has been reduced (December 2017), but the target study population was extended to 3000 patients. The characteristics of the population are now better defined: patients seen in an imaging lab, which will include patients undergoing chemotherapy with associated targeted therapy or no targeted therapy, at increased risk of ADRC. In total, 1294 breast cancer patients have been enrolled, and 783 case report forms locked from October 2014 to November 2016. Of these, 481 (61.4%) were seen at first evaluation and 302 (38.6%) while on oncologic treatment with anticancer drugs. Fifty-two patients (17.2%) were not in targeted therapies, 191 (63.3%) were ongoing targeted therapy, and 59 (19.5%) had completed it. Twenty-three (2.9%) patients had a suspected diagnosis and 35 (4.5%) a confirmed diagnosis of ADRC. Arterial hypertension was the most prevalent cardiovascular risk factor (29.2%) followed by diabetes (6.1%). Previous history of heart failure accounted for 0.5%, whereas previous cardiac disease was identified in 6.3% of population.

Conclusion The changes of the original protocol of the COT Registry and first update allow a first glance to the panorama of cardiovascular characteristics of breast cancer patients enrolled.

Keywords Anticancer drug-related cardiotoxicity; Targeted therapy; Heart failure; Cardiac imaging; Arterial hypertension

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The need for a registry on drug-related cardiotoxicity in breast cancer patients

In relation with important advances in adjuvant therapy drugs (anthracyclines, taxanes, and trastuzumab), both disease-free survival and mortality rates of cancer patients have been substantially improved in the last decade.¹ In parallel, the increased survival has brought the problem of anticancer drug-related cardiotoxicity (ADRC) to the attention of both oncologists and cardiologists.^{2,3} The European Society of Cardiology (ESC) timely created a task force for cancer treatments and cardiovascular toxicity, which has published in August 2016 a comprehensive position paper on this issue, under the auspices of the ESC Committee for Practice Guidelines.⁴

In this context, breast cancer-related ADRC, the most common cancer in women,¹ is gaining increasing impact. Age-adjusted 5 year survival of breast cancer patients is known to be about 79%.⁴ A variable proportion of these patients experience ADRC, which can develop during/after anthracycline therapy (cardiotoxicity type 1) or be related to the use of humanized monoclonal antibodies against extracellular domain of HER2, such as trastuzumab (cardiotoxicity type 2).⁵ These two kinds of cardiotoxicity may overlap in breast cancer patients, as these two different classes of drugs are usually administered sequentially. Worthy of note, trastuzumab has shown to have a synergic effect on anthracycline's cardiotoxicity.⁶

To date, the poor data available on presentation and management of breast cancer patients with ADRC are mainly provided by clinical trials, which do not reflect the real world. In addition, information on cardiac imaging and biomarker practice for the detection and follow-up of ADRC into clinical routine in Europe is limited.

Main objectives of the Cardiac Oncology Toxicity Registry

European Association of Cardiovascular Imaging/Heart Failure Association Cardiac Oncology Toxicity (COT) Registry was launched as a multicentre registry, part of the EURObservational Research Programme of the ESC of patients affected by breast cancer referred to imaging laboratories for routine surveillance, suspicion, or confirmation of ADRC. It concerns a comprehensive data collection and evaluation of the current European practice in terms of diagnosis and management of ADRC in breast cancer patients. The COT Registry has been designed to examine clinical signs and symptoms as well as cardiac imaging and treatment practices for ADRC in breast cancer patients in Europe. The cardiac imaging exam actually provides an opportunity to collect clinical information and

detects the onset, progression, or resolution of ADRC. The imaging evaluation concerns mainly an echo exam, which is periodically repeated, including the assessment of standard parameters such as left ventricular (LV) ejection fraction, Doppler-derived diastolic parameters (E/A ratio, E velocity deceleration time, and E/e' ratio), left atrial volume and, optionally, global longitudinal strain according to American Society of Echocardiography/European Association of Cardiovascular Imaging Expert Consensus for Multi-Modality Imaging Evaluation of Adult Patients During and After Cancer Therapy.⁷

The main scopes of the COT Registry include the following: (i) definition of ADRC-related risk factors, clinical phenotypes, and epidemiology; (ii) determination of ADRC outcomes; (iii) report of asymptomatic/symptomatic ADRC rates; (iv) description of ADRC time course; (v) recording of current standards for diagnostic workup (cardiac imaging/biomarkers) and clinical follow-up of those patients; (vi) assessment of treatment changes associated with ADRC and their influence on ADRC; (vii) description of cardioprotective drugs and other therapeutic approaches used for ADRC; and (viii) evaluation of treatment adherence to ESC Guidelines for overt heart failure (HF) or early asymptomatic LV dysfunction.⁸ Rationale and scopes of the COT Registry have been previously published.⁹

Changes from the Cardiac Oncology Toxicity protocol first release

The COT Registry was launched in October 2014 and will last until December 2017 or until 3000 patients are included. After passing through a first short-term pilot phase (1 year recruitment and 1 year follow-up), some changes have been made to the protocol and the electronic case report form (CRF) in order to improve data quality and allow a better analysis of the results. The main protocol changes of the version 2.0 dated 1 October 2015 concerned:

- exclusion/inclusion criteria,
- duration of the registry and study sample size, and
- clarification on the definition of the study population.

The exclusion criterion of isolated breast cancer radiotherapy has been removed, so that the only exclusion concerns the history of a pre-chemotherapy LV dysfunction (LV ejection fraction <50%).

The period for long-term registry recruitment has been reduced (December 2017 instead of June 2018), but the target study population has been extended to 3000 breast cancer patients instead of 700 ADRC, initially established in the protocol version 1.0. The Executive Committee with the approval of the Oversight Committee of the EURObservational

Table 1. List of active contributing countries

Country	Baseline		
	Enrolled patients (%)		Locked CRFs
Austria	10	0.8	7
Belgium	132	10.2	76
China	9	0.7	0
Cyprus	11	0.9	2
France	34	2.6	0
Georgia	12	0.9	11
Germany	28	2.2	17
Greece	38	2.9	29
Italy	662	51.2	481
Malta	19	1.5	10
The Netherlands	1	0.1	0
Norway	13	1.0	9
Portugal	85	6.6	63
Romania	68	5.3	46
Saudi Arabia	99	7.7	16
Serbia	50	3.9	0
Spain	23	1.8	16
Total	1294	100.0	783

CRFs, case report forms.

Research Programme has reserved the chance to continue the registry going further the declared deadline.

Version 2.0 of the protocol better defines the characteristics of the study population. Breast cancer patients seen in an imaging lab (echo or nuclear cardiology) for routine surveillance of LV function or suspected ADRC or confirmed LV dysfunction are enrolled in the registry. Following these criteria, the study population will include patients undergoing chemotherapy with associated targeted therapy (e.g. trastuzumab) or no targeted therapy, at increased risk of ADRC.

The outpatients' visits are performed according to the usual practice of the participating centres as established in the version 1.0. However, the 1 month follow-up visit has been abolished in order to introduce in the protocol a scheduled 3 month follow-up visit after enrolment, which reflects the common clinical practice in European imaging laboratories. Accordingly, data on morbidity and mortality at 3, 6, and 12 months after the entry visit will be collected.

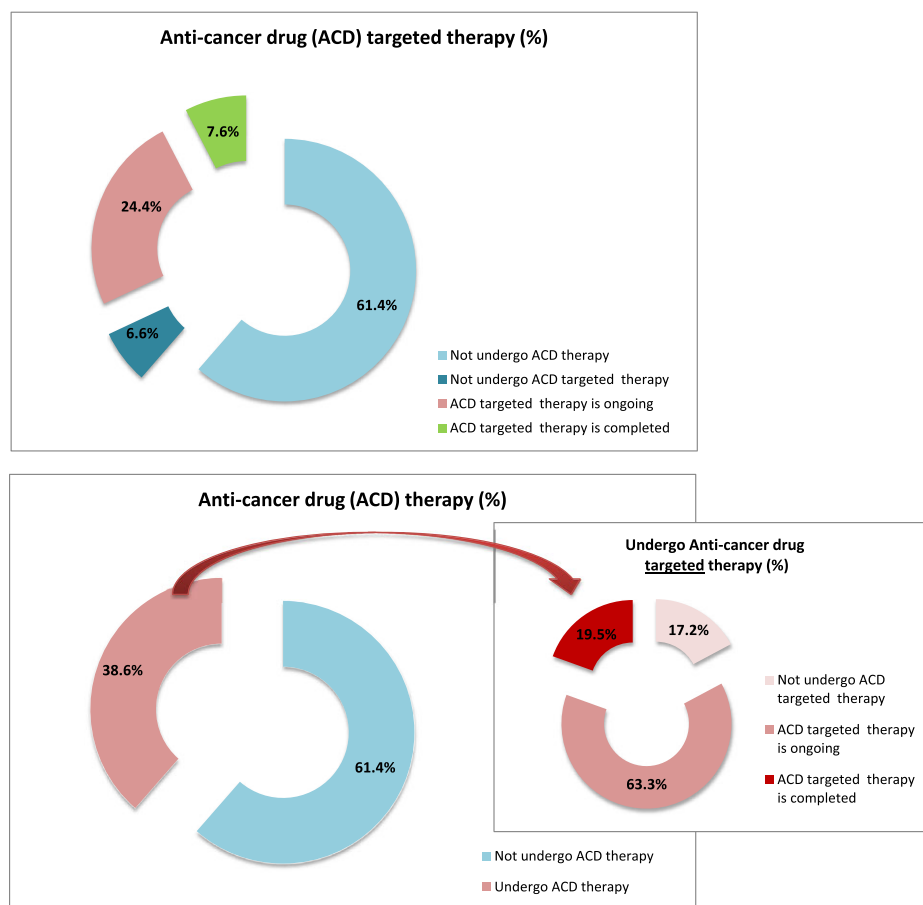
Figure 1 Percentage of patients on anticancer drug therapy (upper panel) and of those on anticancer targeted therapy (ongoing or completed) in breast cancer patients of the Cardiac Oncology Toxicity Registry (lower panel).

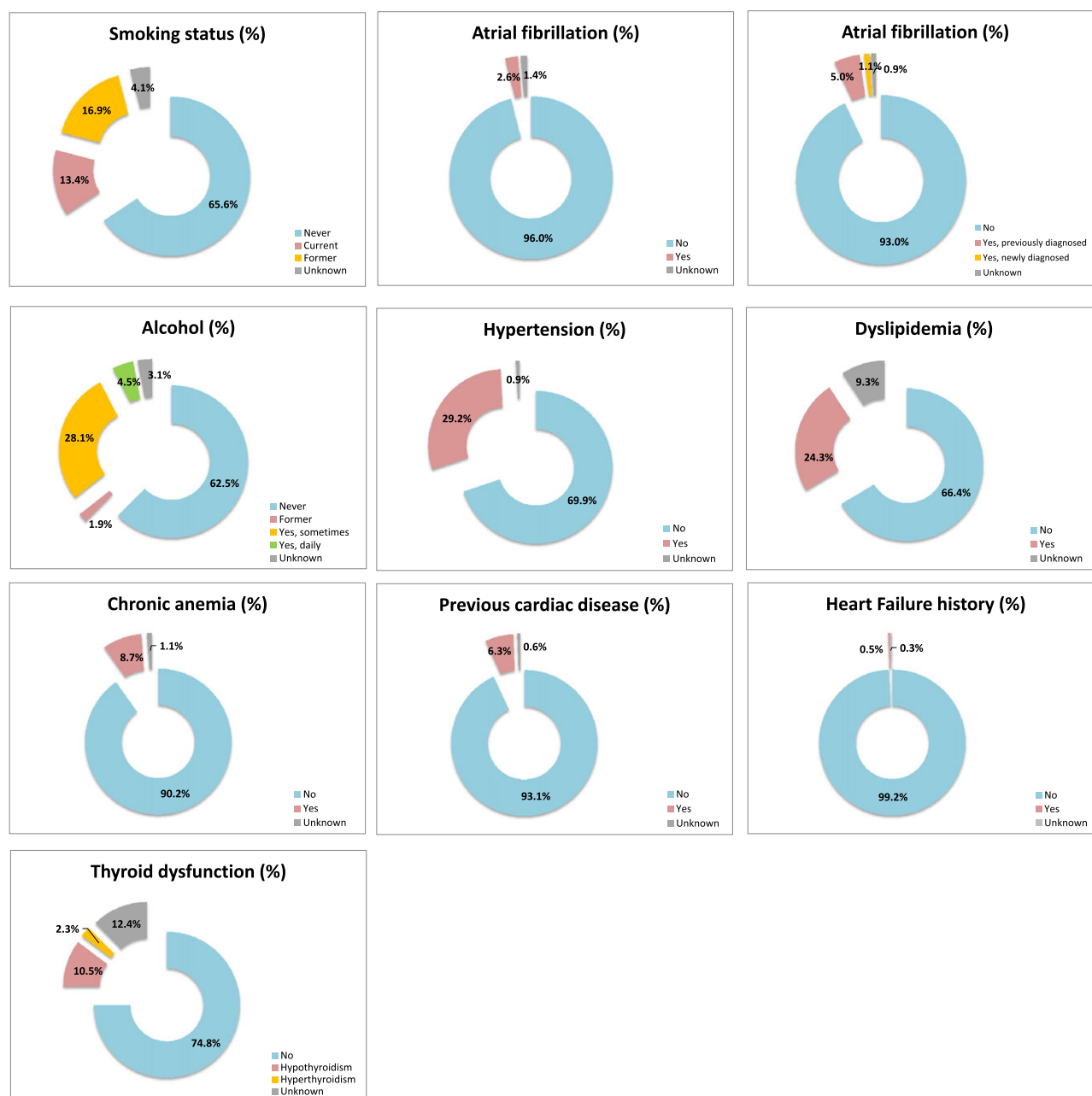
Table 2. Population synthesis regarding ADRC in the Cardiac Oncology Toxicity Registry

Type of ADRC	n	%
Surveillance of LV function	725	92.6
Confirmed diagnosis of ADRC	35	4.47
Suspected diagnosis of ADRC	23	2.9
Total	783	100.0

ADRC, anticancer drug-related cardiotoxicity; LV, left ventricular.

Information on recruitment and preliminary results

The first patient visit of the COT Registry occurred in October 2014. In 27 registered countries, 110 centres were registered in Europe and countries outside Europe such as Argentina, Brazil, Saudi Arabia, China, and India. Among these, 17 countries

Figure 2 Prevalence of arterial hypertension, diabetes mellitus, smoking status, dyslipidemia, history of heart failure, and previous cardiac disease in the initial population of the Cardiac Oncology Toxicity Registry. The term 'unknown' refers to patients in whom the specific information was not collected.

(68%) and 58 centres (53%) are actually active. The leading enrolling countries are Italy (51.2%) followed by Belgium (10.2%), Saudi Arabia (7.7%), Portugal (6.6%), and Romania (5.3%). Globally, 1294 breast cancer patients have been enrolled, and 783 CRFs locked (CRF can be locked when all oncologic and cardiologic parameters are collected for individual patients) making possible a preliminary analysis of the results (*Table 1*).

Of these 783 patients, 481 (61.4%) were seen at their first evaluation, that is, referred to the cardiac imaging lab for a baseline (pre-anticancer drug therapy) evaluation, whereas 302 (38.6%) were already on oncologic treatment with anticancer drug therapy; in this latter group, 52 patients (17.2%) were not in targeted therapies (mainly anthracyclines), 191 (63.3%) were ongoing targeted therapy, and 59 (19.5%) had completed it (*Figure 1*). *Table 2* summarizes the hitherto population synthesis regarding the detected ADRC in the COT Registry: 23 (2.9%) patients had a suspected and 35 (4.5%) a confirmed diagnosis of ADRC. In the overall population, arterial hypertension was the most prevalent cardiovascular risk factor (29.2%) followed by diabetes mellitus (6.5%), whereas smoking status (13.4%) and dyslipidemia (24.3%) appeared rarely. Previous history of HF (before the beginning of anticancer drug therapy) accounted for 0.5%, whereas previous cardiac disease was identified in 6.3% of the study population (*Figure 2*).

Implications

Changes of electronic CRF in version 2.0 of the COT Registry were performed to improve the data collection and provide the possibility of more comprehensive analyses and better interpretation of the results. In particular, these changes reflect more appropriately the common clinical practice in European countries. The inclusion of patients undergoing isolated breast cancer radiotherapy enlarges the sample size of the study population, again being much more representative of the breast cancer population in the real world. Radiotherapy is in fact often associated with drug therapy in the management of these patients. The main effects of radiotherapy-induced toxicity involve vascular system (coronary and carotid arteries), myocardium itself, pericardium, heart valves, and conduction system, leading to possible multiple clinical aspects of cardiac damage, mainly coronary artery disease, HF, and arrhythmias.^{10–13}

The analysis of preliminary results highlights the type and rate of ADRC as well as the prevalence of cardiovascular risk factors in the study population.

The combined rate of suspected and confirmed ADRC was 7.4%, a rate that should not be under evaluated. This finding is valuable as it has been derived by real-world

evidence. This is actually an important advantage of a registry in comparison with clinical trials. Data derived from clinical trials are expected to underestimate the 'true' frequency of HF in cancer patients for two main reasons: first, patients at risk of HF based on previous cardiac diseases are excluded; second, cancer trial participants who developed HF symptoms could drop out of chemotherapy trials without undergoing follow-up. Even in epidemiologic studies, HF due to ADRC may be underestimated because of the long interval between chemotherapy and clinical findings.

Other important data involve the prevalence of cardiovascular risk factors observed in the study population of COT Registry. The relatively high rate of arterial hypertension (29.3%) combined with the 24% rate of dyslipidemia and 5% rate of diabetes mellitus points out a possible common denominator of metabolic syndrome and cancer. This association has already been reported,¹⁴ as insulin resistance is associated with HF.¹⁵ Arterial hypertension has previously been identified as one of the main factors for ADRC.^{16,17} The rate of previous cardiac disease was 6.3%, another finding, which confirms previous investigations.¹⁶ The increasing number of the COT study population might influence the determinants of ADRC because of factors such as age, previous cardiac irradiation, and especially coronary artery disease.

In conclusion, changes of the original protocol of the COT Registry and first update allow a first glance to the panorama of cardiovascular characteristics of breast cancer patients enrolled. A larger population will be needed to provide information on outcome of ADRC, to describe the time course of ADRC according to the beginning of chemotherapy, and to design the exact picture of the European standards for diagnostic workup and clinical follow-up of these patients as well as the treatment adherence to ESC Guidelines for overt and asymptomatic HF. Worthy of note, final release and completion of the COT Registry will represent a possible model to collect cardiac information on diagnosis and management of ADRC in other types of tumours.

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Executive Committee

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HFA: Stefan Anker (Co-Chair), Dimitrios Farmakis, Gerasimos Filippatos

Oncologist: Guy Jerusalem

Conflict of interest

None declared.

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Supporting information

Supporting information may be found in the online version of this article.

Appendix S1. Executive Committee, EORP Team and Investigators.

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