



Original Research

Anthracycline-induced cardiotoxicity: A multicenter randomised trial comparing two strategies for guiding prevention with enalapril: The International CardioOncology Society-one trial



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Abstract Background: Troponin changes over time have been suggested to allow for an early diagnosis of cardiac injury ensuing cancer chemotherapy; cancer patients with troponin elevation may benefit of therapy with enalapril. It is unknown whether a preventive treatment with enalapril may further increase the benefit.

Methods: The International CardioOncology Society-one trial (ICOS-ONE) was a controlled, open-label trial conducted in 21 Italian hospitals. Patients were randomly assigned to two strategies: enalapril in all patients started before chemotherapy (CT; ‘prevention’ arm), and enalapril started only in patients with an increase in troponin during or after CT (‘troponin-triggered’ arm). Troponin was assayed locally in 2596 blood samples, before and after each anthracycline-containing CT cycle and at each study visit; electrocardiogram and echocardiogram were done at baseline, and at 1, 3, 6 and 12-month follow-up. Primary outcome was the incidence of troponin elevation above the threshold.

Findings: Of the 273 patients, 88% were women, mean age 51 ± 12 years. The majority (76%) had breast cancer, 3% had a history of hypertension and 4% were diabetic. Epirubicin and doxorubicin were most commonly prescribed, with median cumulative doses of 360 [270–360] and 240 [240–240] mg/m², respectively. The incidence of troponin elevation was 23% in the prevention and 26% in the troponin-triggered group ($p = 0.50$). Three patients (1.1%) -two in the prevention, one in the troponin-triggered group-developed cardiotoxicity, defined as 10% point reduction of LV ejection fraction, with values lower than 50%.

Interpretation: Low cumulative doses of anthracyclines in adult patients with low cardiovascular risk can raise troponins, without differences between the two strategies of giving enalapril. Considering a benefit of enalapril in the prevention of LV dysfunction, a troponin-triggered strategy may be more convenient.

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1. Introduction

Cardiotoxicity is a potential, feared complication of cancer chemotherapy (CT) and may induce undertreatment and subsequent loss of clinical effectiveness, with impact on the patient’s morbidity, mortality and quality of life, independently of the oncologic prognosis [1]. It usually progresses from cardiomyocyte injury to silent left ventricular dysfunction (LVD) which often becomes symptomatic and irreversible. As a result, its prevention and early detection are of paramount importance in cancer patients [2].

At present, anthracyclines are still a major component of CT regimens thanks to their beneficial effects on survival in different solid cancers (mainly breast cancer) and lymphomas [3]. However, these medications are frequently responsible for cardiotoxicity which has been reported to occur mostly in the first year after CT [4].

Measurement of cardio-specific biomarkers can be useful for early identification, assessment and monitoring of cardiotoxicity. The role of cardiac troponins as indicators of early anthracycline-induced cardiotoxicity, and their ability to predict subsequent LVD has been extensively studied [5,6]. Previous studies suggest that

Research in context

Evidence before this study

We searched PubMed and Embase for clinical studies on anthracyclines, in which troponins were used/studied as read-out of cardiac toxicity. We retrieved 171 clinical studies published in English between Sep 1995 and Nov 2017. Out of the 171, 31 were randomised clinical studies. Search terms were ‘anthracyclines’ and ‘troponin’. Troponin I or T were used as markers of cardiotoxicity either in cohort studies or in controlled clinical trials. Along the same line of research, cardiac troponin was tested as a biomarker to help the clinician in early identification of patients with subclinical cardiac toxicity, thus allowing for protective interventions to be more effective. Several clinical studies showed the protective effects of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II–receptor blockers and beta-blockers in improving left ventricular dysfunction and/or clinical heart failure after cancer chemotherapy (CT). Most of these studies were of small size, monocentric, and cardioprotective drugs were started at the beginning or right before CT. The possibility of identifying patients at high risk of developing cardiotoxicity by a simple test such as measuring circulating troponin was reported to be an effective tool for identifying candidates to cardiac protective therapy with enalapril among those treated with anthracyclines in a monocentric study. However, no data were available comparing the effect of a primary versus a secondary prevention strategy for anthracycline-related cardiotoxicity, using serial measurements of troponins in plasma as guidance. For this reason, we designed the International CardioOncology Society-one trial (ICOS-ONE) to identify the most effective and convenient strategy of targeting anthracycline-related cardiotoxicity with an ACE-inhibitor by comparing a non-selective preventive strategy (i.e. all patients started CT and enalapril) with a selective strategy (i.e. only patients with troponins rise are started on enalapril).

Added value of this study

To the best of our knowledge, the ICOS-ONE study is the first large multicenter randomised trial that compared enalapril started in all patients at the beginning of their first (CT; ‘prevention’ arm), with enalapril started only in patients with an increase in troponin during or after CT (‘troponin-triggered’ arm). Incidence of troponin elevations peaked at 1 month after CT and was similar in the 2 arms: 26% in prevention and 23% in troponin triggered. However, only three patients (1.1%) -two in the prevention, one in the troponin-triggered group- developed cardiotoxicity, defined as 10% point reduction of LV ejection fraction, with values lower than 50%. The effective collaboration between cardiologists and oncologists, within each of the 21 centres participating to the ICOS-ONE network, contributed to a fair comparison of biomarker-based strategies, reducing possible biases.

Implications of all the available evidence

No differences between the two enalapril strategies, preventive or troponin triggered, in preventing myocardial injury as detectable by troponin increase within the first month or so after CT were observed. Patients included in ICOS-ONE show a very low 1-year incidence of clinically relevant LV dysfunction after CT with anthracyclines as far as they do not have concomitant heart disease, normal troponin at baseline and receive low cumulative doses of anthracyclines. Considering a benefit of enalapril in the prevention of LV dysfunction, a troponin-triggered strategy appears more convenient.

troponin changes over time allow accurate cardiac risk stratification after CT. Patients without troponin elevation do not develop LVD and present a very low incidence of adverse cardiac events in the first year after CT. Troponin-positive patients however, particularly those with a persistent rise, are at high risk of LVD and of major adverse cardiac events [7,8]. Thus, the possibility of identifying patients at high risk of cardiotoxicity on the basis of cardiac troponins offers an opportunity for developing pharmacological strategies aimed at preventing LVD in selected patients. Enalapril, started after the first troponin increase and continued for one year, prevented the development of LVD and of cardiac events

after CT [9]. However, as troponin may increase at various intervals after CT, possibly on account of differences in its release kinetics in response to different treatments and schedules, repeated blood samples are usually required to pick-up any increase. This is a limitation for using a troponin-based preventive approach in clinical practice [10] but, a primary prevention strategy—i.e. enalapril extended to all patients scheduled for cardiotoxic CT, not only those with an increase in troponin—may overcome this limitation. Moreover, as activation of the cardiac renin-angiotensin system (RAS) may play a role in anthracycline-induced cardiomyopathy in preclinical studies [11–13], preventive treatment

with enalapril could avert the rise of troponin and the need for long-term cardiac surveillance of these patients.

The aim of the International CardioOncology Society-one (ICOS-ONE) trial was to investigate whether enalapril, started in all patients before CT, prevented the rise of troponin and the possibly ensuing LVD ('prevention' arm), when compared with a strategy based on enalapril started only in patients with an increase in troponin during or after CT ('troponin-triggered' arm). This is the first prospective multicenter randomised trial investigating this approach.

2. Methods

2.1. Study design

ICOS-ONE was a controlled, open-label, multicenter, phase III trial conducted in 21 Italian hospitals (full list in the [Appendix](#)).

2.2. Study population

Patients ≥ 18 years old, with a first diagnosis of cancer and indication for first-line therapy with anthracyclines were eligible. The complete design of the ICOS-ONE trial is described in detail in the Data Supplement, including all inclusion and exclusion criteria, randomisation, monitoring, and follow-up. The trial complied with the Declaration of Helsinki. All patients gave written informed consent. The protocol was approved by Regulatory Agencies and local Ethics Committees and was registered in the ClinicalTrials.gov registry (NCT01968200) before starting (EudraCT Number: 2012-002248-26).

2.3. Study protocol

Eligible patients were randomly assigned in a 1:1 ratio to one of the trial strategies by an automated web-based system. In the 'prevention group' enalapril was started at the time of first cycle of CT. In the 'troponin-triggered group', enalapril was started only in patients with troponin elevation during CT. In both groups, the starting dose was 2.5 mg twice a day. The dose was doubled every two weeks, as tolerated, according to a titration protocol, with recommended monitoring blood pressure, serum creatinine and potassium. The target dose was 10 mg twice daily, to be continued until the end of the 1-year follow-up.

After randomisation, patients were examined at each CT cycle, then 1, 3, 6 and 12 months after the last cycle. Routine laboratory and troponin tests were done before and right after each anthracycline CT cycle and at each study visit; electrocardiogram and echocardiogram were done at baseline, and at 1, 3, 6 and 12-month follow-up. Echocardiography, troponin assay and statistical methods are reported in the data supplement.

2.4. Primary end-point

The primary outcome was the incidence of troponin elevation above the threshold indicated by the manufacturer of the assay used by the local laboratories, at any time during the trial up to 1 year.

2.5. Secondary end-points

Secondary end-points were LVD, defined as a reduction of LV ejection fraction (LVEF) by 10%, with values lower than 50%, death from cardiovascular causes, death from any cause, hospitalisation for cardiovascular causes, major adverse cardiovascular events.

2.6. End-point validation

All primary and secondary end-points were adjudicated by an independent committee (see [Appendix](#)) blind to patient identification and strategy assigned.

3. Results

A total of 273 patients were enrolled from May 2013 to May 2015 in 21 Italian hospitals; 136 patients were randomised to the prevention arm, and 137 to the troponin-triggered arm. Baseline and clinical characteristics of the patients were similar in the two groups ([Table 1](#)). In all, 88% of patients were women, mean age 51 ± 12 years. The majority (76%) of patients had breast cancer, 3% presented a history of hypertension and 4% were diabetic.

The median number of cycles of anthracyclines was 4 [3–4], delivered over 65 [63–76] days. Epirubicin and doxorubicin were the most commonly prescribed anthracyclines, with a median cumulative dose of 360 [270–360] and 240 [240–240] mg/m², respectively. During the trial, 63% of the patients with breast cancer were treated with taxanes and 22.5% with trastuzumab ([Table 1](#)); 2 (0.8%) patients were treated with a tyrosine-kinase inhibitor, imatinib. The prescription rates of these medications were no different in the two groups ([Table 1](#)).

Twelve-month follow-up after the end of CT was concluded for the last patient enrolled on 5 August, 2016, and the median time between randomisation and end of follow-up was 440 [418–474] days.

3.1. Study drug tolerability and safety

The median daily dose of enalapril, calculated over the actual treatment duration, was 5 mg [2.5–17.3], with 80% of the patients on 5 mg/day. Enalapril was well tolerated in most patients. Untoward side-effects occurred in 19/136 (14.0%) of the 'prevention group' and in 3/137 (2.2%) of the 'troponin-triggered group' ($p < 0.001$); this later becomes 8.3% when calculated for the 36 patients who were started on enalapril according to protocol ([Table 2](#)). The

Table 1
Patient's baseline and clinical characteristics.

Patients' characteristics	Total (n = 273)	Prevention (n = 136)	Troponin-triggered (n = 137)	p-value
Demographics				
Women (%)	241 (88.3)	120 (88.2)	121 (88.3)	0.98
Age (year, mean ± SD)	51.3 ± 11.92	50.8 ± 11.8	51.8 ± 12.04	0.48
≤40 years (No. (%))	44 (16.1)	20 (14.7)	24 (17.5)	0.53
BMI (kg/m ² , mean ± SD)	24.53 ± 4.05	25.0 ± 4.1	24.1 ± 4.0	0.07
Heart Rate (bpm, mean ± SD)	75.58 ± 11.26	74.7 ± 10.7	76.4 ± 11.8	0.24
SBP (mmHg, mean ± SD)	122.52 ± 11.69	122.6 ± 11.7	122.4 ± 11.8	0.91
DBP (mmHg, mean ± SD)	75.57 ± 7.71	74.9 ± 7.4	76.2 ± 8	0.21
LVEF (%), mean ± SD)	63.7 ± 6.0	63.5 ± 5.9	63.9 ± 6.1	0.55
Clinical history, No. (%)				
Hospitalisation in the last year	140 (51.3)	67 (49.3)	73 (53.3)	0.51
Hypertension	7 (2.6)	4 (2.9)	3 (2.2)	0.72*
Dyslipidemia	17 (6.3)	6 (4.4)	11 (8.1)	0.21
Diabetes	11 (4)	6 (4.4)	5 (3.7)	0.75
Current smoker	44 (16.2)	20 (14.7)	24 (17.7)	0.58
Ex-smoker	35 (12.9)	20 (14.7)	15 (11.0)	
Stroke	2 (0.7)	0	2 (1.5)	0.50*
Paroxysmal atrial fibrillation	2 (0.7)	0	2 (1.5)	0.50*
Type of cancer, No. (%)				
Breast cancer	207 (75.8)	103 (75.7)	104 (75.9)	0.17*
Acute leukaemia	29 (10.6)	14 (10.3)	15 (11.0)	
Non-Hodgkin's lymphoma	26 (9.5)	11 (8.1)	15 (11.0)	
Hodgkin's lymphoma	8 (2.9)	7 (5.2)	1 (0.7)	
Lymphoma, unspecified type	1 (0.4)	0	1 (0.7)	
Sarcoma	1 (0.4)	1 (0.7)	0	
Other	1 (0.4)	0	1 (0.7)	
Anthracyclines used during the study				
Cumulative anthracycline dose,[#] Median [Q1–Q3] (mg/m ²)	180 [135–240]	180 [135–240]	180 [135–240]	0.80**
Type of anthracycline, No. (%)				
Epirubicin	125 (46)	65 (48.2)	60 (43.8)	0.29*
Doxorubicin	112 (41.2)	55 (40.7)	57 (41.6)	
Idarubicin	21 (7.7)	12 (8.9)	9 (6.6)	
Daunorubicin	9 (3.3)	2 (1.5)	7 (5.1)	
Doxorubicin liposomal	5 (1.8)	1 (0.7)	4 (2.9)	
Patients with breast cancer treated with taxane-based chemotherapy and trastuzumab				
Taxane	126/200 (63.0)	62/98 (63.3)	64/102 (62.8)	0.94
Trastuzumab	45/200 (22.5)	18/98 (18.4)	27/102 (26.5)	0.17

Abbreviations: BMI, body-mass index; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

*Fisher's test; **Kruskal–Wallis test; # Cumulative anthracycline dose was calculated by converting the different anthracyclines in terms of doxorubicin equivalents [34]; when the latest converting algorithm by ESC 2016 [2] was applied, cumulative anthracycline doses were 240 [189–250] all, 240 [189–252] prevention, and 240 [168–252] troponin-triggered (p = 0.48).

most common reason for enalapril discontinuation was hypotension and cough (Table 2). Patients who experienced cough, were given valsartan at the dose of 40 mg twice daily, up-titrated to 160 mg/12h.

During follow-up, bisoprolol was prescribed in 20 (15%) in the 'prevention group', and in 10 (7%) in the 'troponin-triggered group'; the reasons for its prescription were sinus tachycardia, withdrawal of enalapril for symptomatic hypotension, and cardiotoxicity.

No Serious Adverse Drug Reactions or Suspected Unexpected Serious Adverse Reactions were reported during the study.

3.2. Primary end-point

A total of 2596 troponin assessments were done; on average slightly less than 10 per patient. Table 3 lists the

types of troponin used for measuring troponins in each hospital. The cumulative number of patients with first elevation of troponin during the study was 67 (24.5%); median time to first increase was 25 days after the end of CT, and 100 days after randomisation (Fig. 1). There was no difference between the groups in the proportion of patients with a first high troponin level, 23% (31) in the prevention group and 26% (36) in the troponin-triggered group (p = 0.50), or in the time to the first troponin elevation (HR: 1.13, 95% CI 0.70–1.83; p for log-rank test = 0.61). Almost all new cases in both groups (60 out of 67, 89.6% overall) were reported within the first month after the end of CT, half occurring during CT. Almost half the cases had only one troponin rise. The cumulative dose of anthracycline was significantly higher in patients with at least one rise in troponin (Table 4; p = 0.0006). The median level of the

Table 2
Adverse drug reactions.

Patients' characteristics	Total	Prevention	Troponin-triggered	P value
	(n = 172)	(n = 136)	(n = 36 ^a)	
	No. (%)	No. (%)	No. (%)	
Overall ADR, patients	22 (12.8)	19 (14.0)	3 (8.3)	0.42**
- Allergic reaction	3 (1.7)	3 (2.2)	0	
- Other:	20 (11.6)	17 (12.5)	3 (8.3)	
Cough	6	6 (4.4)	0	
Hypotension	8	7 (5.1)	1 (2.8)	
Visual disturbance, headache	1	1 (0.7)	0	
Lower limb oedema	1	0	1 (2.8)	
Lipothymia	1	1 (0.7)	0	
Neutropaenia	1	0	1 (2.8)	
Night sweats & palpitations	1	1 (0.7)	0	
Hyperkalemia	1	1 (0.7)	0	

One patient in the prevention arm had two ADRs.

Abbreviation: ADR, adverse drug reaction.

**Fisher's test.

^a Thirty-six patients had high troponin and therefore had to be treated per protocol; 101 patients in this strategy did not receive any ACE-inhibitor and were therefore excluded from the analysis.

first elevation of troponin was 40% [22–90] above the ULN in the prevention group and 33% [18–50] in the troponin-triggered arm ($P = 0.17$). There were significantly more troponin rises among patients treated with doxorubicin-based CT than in those with epirubicin: respectively 44 (39%) and 19 (15%) ($p < 0.0001$).

3.3. Secondary end-points

The incidence of cardiac events was very low in both groups (Table 5). Three patients (1.1%), two in the prevention group, one in the troponin-triggered group, developed cardiotoxicity, defined as a 10% point reduction of LVEF, with values lower than 50%. Only one patient was hospitalised for a cardiovascular event, acute pulmonary embolism (prevention group). One patient in the troponin-triggered group had acute pulmonary oedema after fluid overload during hemopoietic stem cell transplantation. Mean LVEF during follow-up was similar to baseline values and between study arms (Supplemental Fig. 1). The two study groups were also similar in their maximum percentage changes in LVEF during chemotherapy and 1-year follow-up (not shown).

During the 1-year follow-up, 10 patients died (3.7%), 8 in the prevention arm and 2 in the troponin-triggered arm (Table 5). These deaths were all non-cardiovascular and were related to the progression of cancer (70%) or

infection (30%). One patient in the prevention group and one in the troponin-triggered group experienced an episode of paroxysmal atrial fibrillation. One other patient had an episode of sinus bradycardia, reported as an effect of bisoprolol.

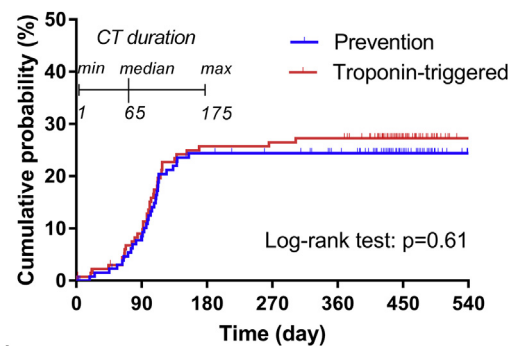
The distribution of patients is illustrated in Fig. 2, and details of per protocol analysis are reported in the data supplement.

4. Discussion

To the best of our knowledge, ICOS-ONE is the first multicenter randomised trial that compared two strategies to prevent anthracycline-induced cardiotoxicity with enalapril. One strategy was designed to prevent the troponin rise induced by anthracyclines by starting cardioprotective treatment in all patients together with

Table 3
Types of troponin assayed.

Type of troponin, No. (%)	No. of assays (2596)
Troponin T	133 (5.1)
High-sensitive troponin T	372 (14.3)
Troponin I	1289 (49.7)
High-sensitive troponin I	796 (30.7)
Not specified	6 (0.2)



Patients at risk	Time (day)						
	0	90	180	270	360	450	540
Prevention	136	117	94	91	85	40	6
Troponin-triggered	137	120	97	97	95	45	10

Fig. 1. Kaplan–Meier survival curves for troponin elevation. Cumulative probability of troponin above the upper limit of normal in the intention-to-treat population, by study arms. Time 0, randomisation.

Table 4
Number of high troponin samples according to type and cumulative anthracycline dose.

Patients' characteristics	No raised Tn (206 patients)	Only 1 raised Tn sample (31 patients)	>1 raised Tn samples (36 patients)	P-value
Epirubicin, No. (%)	106 (52)	10 (32)	9 (25)	0.0016
Doxorubicin, No. (%)	68 (33)	20 (64)	24 (67)	
Idarubicin, No. (%)	5 (2)	0	0	
Daunorubicin, No. (%)	18 (9)	0	3 (8)	
Doxorubicin liposomal, No. (%)	8 (4)	1 (3)	0	
Cumulative anthracycline dose ^a (median [Q1-Q3], mg/m ²)	180 [135–240]	240 [180–240]	240 [180–270]	0.0006

^a Cumulative anthracycline dose was calculated by converting the different anthracyclines in terms of doxorubicin equivalents [34].

Table 5
Secondary end-points in the total study population, in the prevention and troponin-triggered groups.

Patients' characteristics	Total (n = 273)	Prevention (n = 136)	Troponin-triggered (n = 137)	P value ^a
All-cause mortality, No. (%)	10 (3.7)	8 (5.9)	2 (1.5)	0.06
Cardiovascular mortality, No. (%)	0	0	0	–
Non-cardiovascular mortality, No. (%)	10 (3.7)	8 (5.9)	2 (1.5)	–
Tumour	7 (2.6)	6 (4.4)	1 (0.7)	–
Infection	3 (1.1)	2 (1.5)	1 (0.7)	–
Left ventricular dysfunction, No. (%)	3 (1.1)	2 (1.5)	1 (0.7)	1.00
First CV hospitalisation, No. (%)	1 (0.4)	1 (0.7)	0	0.50
Acute pulmonary embolism, No. (%)	1 (0.4)	1 (0.7)	0	–
Other CV events	1 (0.4)	0	1 (0.7)	1.00
Heart failure, No. (%)	0	0	0	–
Stroke, No. (%)	0	0	0	–
Acute coronary syndrome, No. (%)	0	0	0	–
Acute pulmonary oedema, No. (%)	1 (0.4)	0	1 (0.7)	1.00
Arrhythmias requiring treatment, No. (%)	3 (1.1)	1 (0.7)	2 (1.5)	1.00

^a Fisher's test.

CT; the second strategy was to use enalapril only for selected patients who had an increase in troponin during or after CT. The main finding was that the incidence of troponin rise during anthracycline-treatment—the primary end-point—was the same in the two groups independently of enalapril treatment.

It was previously reported that a rise in troponin I is a risk marker for the development of LVD after high-dose anthracycline CT, whereas patients with no increase had a very low incidence of LVD (1% versus 39%) [7,8,14]. In the same clinical setting, a single-centre randomised trial reported that early treatment with enalapril after evidence of myocardial cell injury—revealed by an increase in troponin I—and continued for one year, prevented LVD, and the associated adverse clinical events (2% versus 52%). Though these findings were not formally tested in the present multicenter trial, it can be concluded that this approach—previously proposed—[9] is reproducible and feasible in several clinical settings, with different troponin assays and cut-offs. A possible limitation for using this approach in clinical practice, however, is the need to collect blood samples several times to document an increase of this marker [10].

A vital point about the use of troponin in the early detection of cardiotoxicity is the timing of sampling. After acute ischaemic myocardial injury troponins show a specific kinetic profile [15] whereas the time course of troponin changes after CT is more variable, and less clearly defined. This may be due to the differences in troponin release kinetics in response to various treatment schedules, or different analytical sensitivities and thresholds of normality for cardiac troponin measurements, and different cardiotoxic mechanisms. However, given the very high predictive value of repeated normal troponin values observed in previous studies [8], this strategy might be justified and cost-effective when it permits the exclusion of most patients from long-term monitoring with expensive imaging. On the other hand, cardioprotective treatment for all patients scheduled for potentially cardiotoxic therapy (primary prevention) does not require troponin monitoring, but may be demanding in terms of the management of up-titration of the preventive drug, and in safety monitoring, when extended to 100% of patients. It also exposes to possible side-effects patients less likely to develop cardiotoxicity, not requiring any cardioprotective therapy. In the present study, 14% of

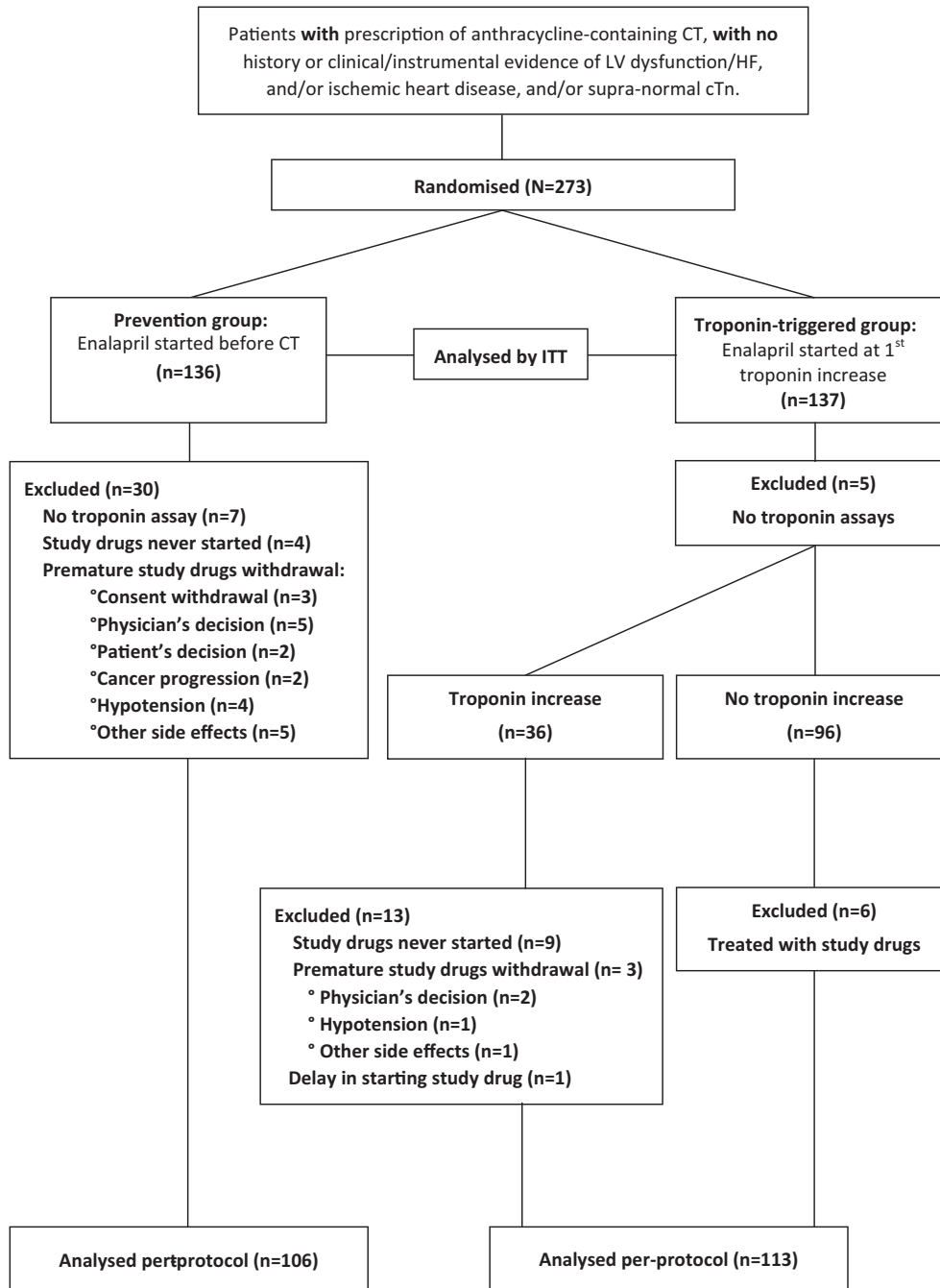


Fig. 2. Consort flow diagram of the ICOS-ONE study. ICOS-ONE, International CardioOncology Society-one trial.

patients in the prevention group developed enalapril-associated side-effects.

In a previous observational prospective study, with a large non-selected population treated with higher doses of anthracyclines, the incidence of LVD at 1-year follow-up was 9% [4]. In other studies, cardiotoxicity ranged from 2.2% to 65%, mainly depending on the total anthracycline dose, and the criteria employed to define cardiotoxicity [11]. The present study indicates that enalapril started either before anthracyclines or only in

patients with a troponin increase during CT is associated with a very low incidence of LVD (1.1%) compared with previous studies, with no differences between the two preventive approaches. Therefore, regardless of the strategy applied, our data indirectly support the benefit of enalapril to prevent anthracycline-induced LVD, although the relatively low doses of anthracyclines may have contributed as well.

Angiotensin-converting enzyme inhibitors (ACEIs) can slow the progression of LVD in different clinical

settings, including anthracycline-induced cardiomyopathy [16–19]. Preclinical data suggest that the RAS plays an important role in anthracycline-induced cardiomyopathy, and that ACEIs may counteract its progression [20–28]. Preclinical studies showed that adriamycin- inhibits ACE activity leading to increases in serum and cardiac concentrations of ACE 20 days after starting anthracycline treatment [29]. In addition, lisinopril started after the end of CT inhibited cardiac ACE activity, significantly reduced mortality and LV remodelling in hamsters [20], thus suggesting a major role of RAS activation in anthracycline-induced cardiotoxicity in animal models. In our study, however, enalapril did not interfere with the anthracycline's direct toxic effect, indicated by the troponin rise. Possible explanations are that the mean dose of 5 mg/day was too little to avoid/protect against myocardial cell injury [30,31], or that the RAS system is activated only after myocardial cell injury has already occurred. In agreement with this latter hypothesis, RAS inhibition by enalapril seems to exert its positive effect by counteracting progression from cell injury to LVD. The similar incidence of troponin increases and the low rate of LVD in the two study groups here seems to support this.

Other studies examined troponin increases during anthracycline-cardiotoxicity prevention. In the OVERCOME trial, combined treatment with enalapril and carvedilol was compared with no treatment in patients with malignant hemopathies treated with intensive CT. In the intervention group, enalapril and carvedilol were started simultaneously at least 24 h before the first cycle of CT. The incidence of troponin increase was not statistically different in the intervention group from controls (17% versus 11%; $p = 0.59$) [32]. In the PRADA study, candesartan started before CT did not reduce the increase in circulating cardiac troponin I associated with anthracycline CT in breast cancer patients [33]. These two studies and ours suggest that RAS is not involved in the direct cardiotoxic effect of anthracyclines but does play a role in the myocardial remodelling that occurs after cardiac injury [33].

4.1. Tolerability and safety

Enalapril was very well tolerated by most patients: only 15% of the whole population stopped treatment with the drug; no serious ADR were reported. Very slow and careful drug titration may have contributed to this result, particularly in these patients who are often in poor physical condition as a result of recent CT. However, this kind of management applied in routine practice might be considered demanding when extended to all patients treated with anthracyclines. Given the similar results in the two groups, limiting this approach to selected patients with troponin rise could prove more

cost-effective and more feasible in everyday clinical practice.

4.2. Strengths and limitations of the trial

The two approaches were feasible in 21 different centres thanks to active collaboration between oncologists and cardiologists, despite the burden of the trial (on average 8 clinical visits, 5 echocardiographic examinations and 12 measurements of troponin per patient). The 80% overall compliance with the protocol is definitely encouraging. The study could thus pave the way to future collaborative efforts between the two disciplines, oncology and cardiology.

The effectiveness of the approach based on troponin increase, previously tested only in one centre, has now been replicated in other clinical settings, using locally available troponin assay methods. The high stability of LVEF suggests a less intensive schedule of echocardiographic examinations might be feasible in patients similar to those in this trial.

During follow-up, bisoprolol was added or replaced enalapril in 11% of patients, for different reasons, but the possible impact of a betablocker on LVEF cannot be assessed.

5. Conclusions

The findings of this trial indicate that anthracycline-containing CT can raise troponin even when low cumulative doses of anthracyclines are used in adult patients with low cardiovascular risk. No differences between the two enalapril strategies in preventing myocardial injury as detectable by troponin increase were observed. Considering a benefit of enalapril in the prevention of LV dysfunction, a troponin-triggered strategy appears more convenient.

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Conflict of interest statement

AB, AM, AR, CM, CV, GFC, GR, EB, MG, MTS, SM received funding for travel; FG and received travel and research funding and is associated with consulting or advisory role,; GC received travel funding and honoraria and is associated with consulting, advisory role and speakers' bureau. FC is associated with consulting, advisory role. MS received research funding and RL received research funding and funds for travel.

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Appendix C. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.ejca.2018.02.005>.

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