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Role of hypertension in new onset congestive heart failure in patients receiving trastuzumab therapy for breast cancer

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Background **Adjuvant trastuzumab therapy improves the survival of human epidermal growth factor receptor 2 (HER2)-positive women with early breast cancer (EBC). Trastuzumab-induced cardiotoxicity is not uncommon. In the setting of community patients, the incidence, timing and phenotype of new onset congestive heart failure (CHF) is unknown.**

Methods **Four hundred and ninety-nine consecutive HER2-positive women (mean age 55 ± 11 years) with EBC treated with trastuzumab between January 2008 and June 2009 at 10 Italian institutions were followed-up for 1 year. We evaluated the incidence, time of occurrence, and clinical features associated with CHF. Left ventricular ejection fraction (LVEF) was evaluated by echocardiography at baseline and 3, 6, 9 and 12 months during trastuzumab therapy.**

Results **CHF occurred in 16 patients (3.2%), who were older, more hypertensive and with a higher degree of hypertension in comparison with patients who did not have CHF. All CHF patients had a significant reduction in LVEF with a mean peak of −12% detected at 3-month follow-up. CHF occurred in seven patients (44%) within the 3-month follow-up period, in four patients (25%) between 3 and 6 months, in three patients (19%) between 6 and 9 months and in two patients (12%) between 9 and 12 months. Trastuzumab was discontinued in 10 of 16 patients and re-started in five after LVEF recovery and clinical improvement. New onset CHF was predicted by the presence of hypertension [odds ratio 2.9 (confidence interval 1.1–7.9]).**

Conclusion **New onset CHF seldom occurs in HER2-positive women with EBC, and predominately in the first 6 months of therapy. CHF is associated with a significant reduction in LVEF and is predicted by a history of hypertension.**

J Cardiovasc Med 2014, **15**:141–146

Keywords: breast cancer, congestive heart failure, hypertension, trastuzumab, women

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Received 14 April 2013 **Revised** 17 June 2013
Accepted 14 July 2013

Introduction

Breast cancer is one of the most common tumors affecting women in industrialized countries with a high clinical impact. Over the last two decades, survival rates have increased in these patients due to the effectiveness of new anticancer drugs.[1] However, these drugs, including trastuzumab, are potentially cardiotoxic and may induce left ventricular systolic dysfunction in particular, and, in a minority of patients, overt heart failure (HF). The likelihood of cardiotoxicity during adjuvant chemotherapy is related to the type of therapy, schedule of administration, and other well known risk factors.[2,3] The incidence of trastuzumab-related cardiotoxicity varies widely and ranges from 7[4] to 34%[5,6], including metastatic cancer. In the setting of patients in the community, the incidence, timing, and predisposing factors for congestive heart failure (CHF) are unknown. It has been assessed, even if still under investigation, that there is a relationship between the classic risk factors for cardiovascular (CV) adverse events and the development of chemotherapy-induced CV injury.

The aims of the present study were to assess in a multicenter setting of community patients with early breast cancer treated with trastuzumab-based therapy, without a history of cardiac decompensation: the incidence of new onset congestive heart failure (CHF); the appearance of CHF over time; the clinical variables associated with CHF.

Methods

Data from 499 consecutive patients enrolled in 10 Italian hospitals and cancer institutes between January 2008 and June 2009 were retrospectively reviewed. All patients gave informed consent; the local institutional review boards approved the study protocol. All patients had

1558-2027 © 2014 Italian Federation of Cardiology DOI:10.2459/JCM.0b013e328365afb5

previously been treated with chemotherapy (anthracyclines 88%, cyclophosphamide 89%, taxanes 44%, 5-fluorouracil 46%, neoadjuvant 25%). The trastuzumab treatment protocol, as adjuvant chemotherapy for early breast cancer, consisted of a single loading dose of 8 mg/kg of body weight intravenously, followed by maintenance doses of 6 mg/kg every 3 weeks for 1 year (18 doses in total). An assessment of left ventricular systolic function before starting pretrastuzumab chemotherapy, and subsequently trastuzumab adjuvant treatment, was mandatory for inclusion in the study. Patients who showed a decline of at least 10% in left ventricular ejection fraction (LVEF) before starting adjuvant trastuzumab therapy, compared with LVEF before starting pretrastuzumab chemotherapy, were not included in the registry. For each patient, we collected relevant comorbidities and baseline cardiovascular medications. The condition of 'increased cardiovascular risk' was defined as a 10-year risk of cardiovascular death of at least 5% and recognized according to the European Society of Cardiology guidelines on cardiovascular disease prevention in clinical practice.[7] Diabetes mellitus was diagnosed from WHO criteria (fasting serum glucose $>$ 126 mg/dl or 2-h post challenge serum glucose $>$ 200 mg/dl or the use of hypoglycemic drugs). Dyslipidemia was defined as total cholesterol less than 190 mg/dl and or triglyceridemia less than 150 mg/dl. Hypertension was defined as pharmacologically treated high blood pressure and graded as mild if blood pressure before treatment was more than 140/90 but less than 160/95 mmHg, moderate if it was more than 160/95 but less than 180/105 mmHg, and severe if it was more than 180/105 mmHg.[7] Well-controlled blood pressure, was defined as blood pressure less than 140/90 mmHg. Renal function was assessed by estimation of glomerular filtration rate with the simplified Modification of Diet in Renal Disease equation. For all patients, LVEF was used as the index of left ventricular systolic function and measured at baseline and after 3, 6, 9, and 12 months with Simpson's method on standard two-dimensional echocardiogram, according to Herceptin Adjuvant (HERA) Trial's results and as indicated in the drug package insert.[8] Trastuzumab-related cardiotoxicity was classified in five grades and defined as follows:[9,10]

(1) Grade I: asymptomatic decline in LVEF of less than 10 percentage points from baseline evaluation.
(2) Grade II: asymptomatic decrease in LVEF below 50% or less than 20% from baseline evaluation.
(3) Grade III: symptomatic HF responsive to treatment.
(4) Grade IV: severe or refractory HF or requiring intubation.
(5) Grade V: death related to toxicity.

Before trastuzumab administration, all patients showed no signs or symptoms of HF and had normal LVEF (history of HF and/or LVEF $<$ 55% were considered to be exclusion criteria in our study). During trastuzumab treatment, any diagnosis of HF was based on a comprehensive assessment based on modified Framingham criteria;[11] documented new-onset fatigue and dyspnea, confirmed with cardiomegaly, congestion, or pleural effusions on chest radiograph, and a response to diuretics. All these findings were combined with an evaluation of cardiac structure and function by echocardiography (performed in all patients) and B-type natriuretic peptide (not routinely performed in all participating centers),[12] confirmed by an echocardiographic evaluation of LV systolic and diastolic function. In the presence of cardiotoxicity, the clinical oncologist made the decision to interrupt treatment or re-challenge with trastuzumab. The study protocol was approved by the local institutional review boards.

Statistics

Data are reported as mean values $\pm$ 1 SD. Unpaired Student's test and χ^2 statistics were used for descriptive statistics. Between-group comparisons of continuous and normally distributed variables were performed by the analysis of variance. Multivariate logistic regression analysis was carried out to assess the independent predictors of CHF. The variables included in the model were: age, hypertension, degree of hypertension, glomerular filtration rate, increased cardiovascular risk, pretreatment with doxorubicin. A two-tailed value of $P < 0.05$ was considered statistically significant. SPSS 19.0 Release (SPSS Inc. Chicago, Illinois) was used for statistical analysis.

Results

Four hundred and ninety-nine women (age 55 $\pm$ 11 years) were evaluated in this study. Among these, 128 patients (26%) had a history of arterial hypertension, 30 (6%) had a history of diabetes, 75 (15%) had a history of dyslipidemia and 73 were smokers (14%). The main clinical features and pharmacological treatment of 483 patients who did not experience CHF during the period of observation are shown in Tables 1 and 2 and compared with those of patients who developed CHF during 1-year of follow-up.

Considering the total study population, trastuzumab-related cardiotoxicity was recognized in 133 patients (26.6%). A total of 102 patients (20.4%) showed asymptomatic reduction in LVEF of more than 10% but less than 20% (grade 1); 15 (3%) had an asymptomatic decline of LVEF of more than 20% but less than 50% (grade 2); and 16 patients (3.2%) developed symptomatic CHF (grade 3). No patient had episodes of trastuzumab-related cardiotoxicity of grade IV or V.

Patients who developed congestive heart failure

The main clinical characteristics, oncological treatments, and pharmacological therapy for reducing the cardiovascular risk in these patients are shown in Tables 1 and 2,

Table 1 Baseline characteristic of 499 patients divided according to the development of congestive heart failure at any time during the 1-year trastuzumab chemotherapy

Variable	No CHF ($n=483$)	CHF ($n=16$)	P
Age (years)	55 ± 11	60 ± 11	0.05
Patients aged >60 years [*n* (%)]	150 (31%)	9 (56%)	0.03
Hypertension [*n* (%)]	126 (26%)	8 (50%)	0.03
Degree of hypertension (grade 1–3)	1.65 ± 0.77	2.14 ± 0.90	0.01
Diabetes [*n* (%)]	29 (6%)	1 (6%)	ns
Dyslipidemia [*n* (%)]	72 (15%)	4 (25%)	ns
History of CAD [*n* (%)]	10 (2%)	0	ns
Smoker [*n* (%)]	72 (15%)	1 (6%)	ns
Increased cardiovascular risk [*n* (%)]	72 (15%)	8 (25%)	0.003
Symptomatic arrhythmias [*n* (%)]	19 (4%)	1 (6%)	ns
Valvular disease [*n* (%)]	39 (8%)	3 (18%)	ns
LVEF (%)	64.8 ± 6.0	66.3 ± 6.8	ns
LVEF preanthracyclines (%)	66.0 ± 4.7	65.5 ± 5.5	ns
Hematocrit (%)	38 ± 3	38 ± 3	ns
Hemoglobin (g/dl)	12.9 ± 1.2	12.9 ± 1.1	ns
Creatinine (mg/dl)	0.82 ± 0.16	0.77 ± 0.14	ns
eGFR (ml/min per 1.73 m^2)	82 ± 19	85 ± 22	ns
Therapy for CV risk factors control			
Number of antihypertension drugs	0.42 ± 0.3	0.93 ± 0.7	0.01
ACEi/ARB [*n* (%)]	82 (17%)	7 (44%)	0.007
Diuretics [*n* (%)]	48 (10%)	3 (18%)	ns
β-blockers [*n* (%)]	53 (11%)	5 (31%)	0.01
Calcium antagonists [*n* (%)]	19 (4%)	0	ns
Statins [*n* (%)]	34 (7%)	2 (13%)	ns

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CAD, coronary artery disease; CV, cardiovascular; eGFR: estimated glomerular filtration rate; LVEF, left ventricular ejection fraction.

and were compared with those of patients who did not have CHF. Patients who had CHF were older (60 ± 11 vs. 55 ± 11 years, $P=0.05$), had a major prevalence of hypertension (50 vs. 26%, $P=0.03$) and of more severe degree, and more frequently received ACE-I/ARBs (44 vs. 17%, $P=0.007$) and β-blockers (31 vs. 11%, $P=0.01$) than those who did not have CHF. The main features of each of these 16 patients are detailed in Table 3. Most patients had mild CHF. The adjuvant antitumor treatment was similar between the two study groups. All patients were treated with diuretics, ACE-inhibitors or ARBs and β-blockers according to the European Guidelines for CHF. Ten patients who experienced CHF were not receiving any medication before the onset of heart symptoms, the other six were being treated for hypertension with ACE/ARBs alone, β-blockers or both before trastuzumab administration. As hypertension was a preexisting condition, patients were treated aggressively to control their cardiovascular factors. All CHF patients had received doxorubicin before trastuzumab treatment; at baseline observation they showed a global increased cardiovascular risk in comparison with patients who did not have CHF.

Table 2 Adjuvant antitumor treatments

	No CHF ($n=483$)	CHF ($n=16$)	P
Radiotherapy [n (%)]	290 (60%)	7 (44%)	NS
Chemotherapy			
Anthracyclines (any) [*n* (%)]	420 (87%)	16 (100%)	NS
Type of anthracycline:			
Doxorubicin [*n* (%)]	53 (11%)	4 (25%)	NS
Doxorubicin, mean dose (mg/m^2)	230 ± 55	238 ± 48	NS
Epirubicin [n (%)]	367 (76%)	12 (75%)	NS
Epirubicin, mean dose (mg/m^2)	339 ± 156	317 ± 149	NS
Taxanes (any) [*n* (%)]	232 (48%)	11 (67%)	NS
Type of taxane:			
Paclitaxel [*n* (%)]	101 (21%)	5 (31%)	NS
Docetaxel [*n* (%)]	130 (27%)	6 (38%)	NS
Cyclophosphamide [*n* (%)]	442 (89%)	123 (94%)	NS
5-Fluorouracil [*n* (%)]	227 (47%)	4 (25%)	NS

The appearance of CHF events varied significantly over time. CHF occurred in seven patients (44%) within the 3-month follow-up, in four patients (25%) between 3 and 6 months, in three patients (19%) between 6 and 9 months and in two patients (12%) between 9 and 12 months. The LVEF trend in the group of patients who experienced CHF compared with that of patients who did not during the 1-year trastuzumab therapy was significantly different. The former showed a marked decrease in LVEF during the first 6 month of trastuzumab treatment with a partial recovery during the last 6 months of therapy (Fig. 1). Trastuzumab was discontinued in 10 of 16 patients and re-started safely in five after LVEF recovery.

Multiple logistic regression analysis showed that the presence of hypertension was the only independent variable associated with the occurrence of CHF at any time during the follow-up [odds ratio 2.9 (confidence interval 1.1–7.9)](Fig. 2), after adjustment for age, degree of hypertension, glomerular filtration rate, increased cardiovascular risk, and pretreatment with doxorubicin.

Discussion

In the present study, we demonstrated the following: the incidence of new onset CHF in patients receiving trastuzumab as adjuvant therapy for early breast cancer is 3% per year; the distribution of CHF events during the time is not homogeneous and 70% of events occur within the first 6 months of trastuzumab therapy; and the presence of hypertension is the only clinical predictor of CHF in these patients.

It is well known that target therapies are usually combined with traditional anticancer regimens and this association reduces cancer progression and mortality even if there is a group of patients who experience cardiotoxicity. The anthracyclines themselves are cardiotoxic, but the addition of trastuzumab leads to a synergic increase in the incidence of cardiac symptoms from 17% with doxorubicin alone to 27% in association with trastuzumab.[13] In our population, we experienced cardiotoxicity in about one quarter of cases, and the 3% of patients who developed signs and symptom of CHF when trastuzumab was administered after adjuvant chemotherapy. This represents the first multicenter clinical research that has analyzed actual oncology and cardiology clinical practice. The randomized controlled trials and case-control studies report discrepant

Table 3 Main characteristics of the 16 patients who developed an episode of congestive heart failure during 1-year of trastuzumab treatment

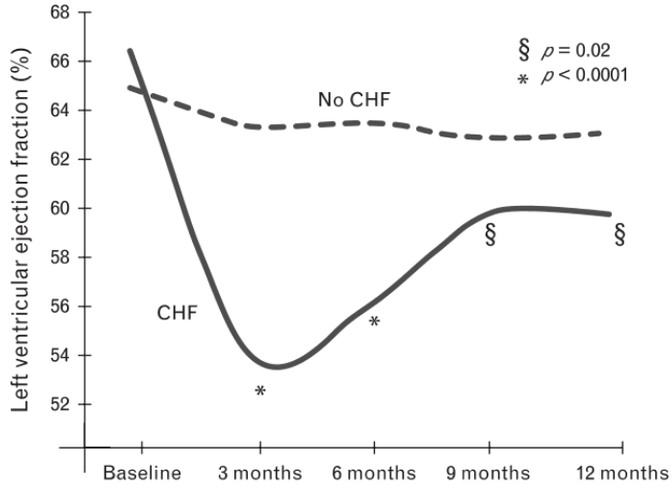
Patient	Age	HT	Degree of HT	Increased CV risk	Previous anthracycline	FE	Impairment NYHA class	Time of CHF onset (months)	Stop Trast	Re-start Trast
1	70	Yes	2	Yes	Yes	77	II	3	Yes	Yes
2	59	–	–	–	Yes	76	II	2	Yes	Yes
3	53	Yes	1	–	Yes	70	II	6	No	–
4	66	Yes	2	Yes	Yes	71	II	9	No	–
5	72	–	–	–	Yes	53	III	4	Yes	No
6	69	–	–	–	Yes	55	IV	1	Yes	No
7	65	Yes	3	Yes	Yes	62	II	5	Yes	No
8	53	Yes	2	–	Yes	65	III	4	No	–
9	49	–	–	–	Yes	70	II	10	No	–
10	37	–	–	Yes	Yes	65	II	5	No	–
11	62	–	–	–	Yes	70	II	3	Yes	No
12	66	Yes	3	Yes	Yes	72	III	7	Yes	Yes
13	41	–	1	Yes	Yes	67	III	3	No	–
14	70	Yes	3	Yes	Yes	61	III	11	Yes	No
15	53	–	–	–	Yes	66	II	2	Yes	Yes
16	67	Yes	2	Yes	Yes	77	II	5	Yes	Yes

CV, cardiovascular; HT, hypertension; NYHA, New York Heart Association; Trast, trastuzumab.

data on the incident of trastuzumab-related cardiotoxicity. In the HERA trials, CHF occurred in 0.2% of controls and 2.1% of trastuzumab treated patients,[10] while CHF occurred in 4.1% (3-year cumulative incidence) of patients enrolled in the NSABP B-31 (national surgical adjuvant breast and bowel project).[14] In the Breast Cancer International Research Group (BCIRG) 006 trial, the incidence of episodes of CHF was 2.0% in the group treated with trastuzumab after anthracyclines.[15] Such discrepancies may be fully explained by large differences in inclusion/exclusion criteria between the studies. One is left to speculate that in patients with a greater and more complex degree of comorbidities, or in those with short expected survival times imposed by the malignancy, hypertension would not provide relevant prognostic information due to a higher effect of other conditions such as diabetes mellitus, renal disease, or advanced liver disease or, more relevantly, the severity of the cancer *per se*. However, the long-term effects of hypertension might influence the development of cardiac diseases such as CHF in patients with relatively low comorbidity and good outcome owing to the early detection of breast cancer. This seems so in our case.

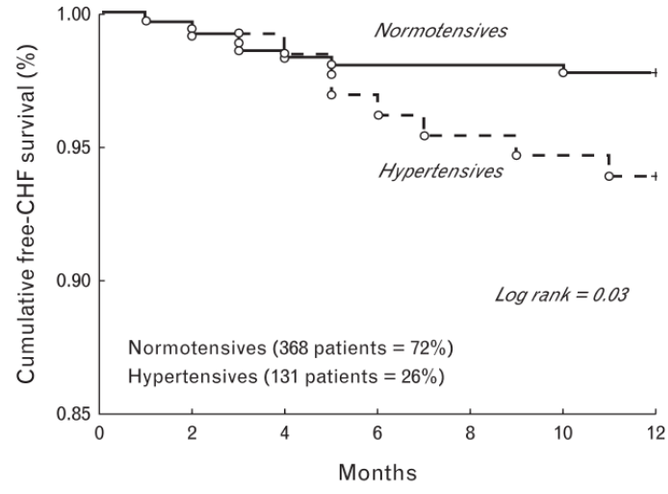
Women with early breast cancer often have coexistent diseases at the time of diagnosis which could influence treatment options and survival.[16,17] An assessment of cardiac risk factors was also required for treated patients included in this study. Previous studies[14,18] have consistently shown that older age and previous anthracycline treatment were independent risk factors for trastuzumab cardiotoxicity and the development of CHF in these patients, and the role of pre-existing hypertension was

Fig. 1



Trend of left ventricular ejection fraction (LVEF) expressed as mean absolute value in the group of patients who experience an episode of congestive heart failure (CHF) compared with that of patients who did not have CHF during 1-year trastuzumab therapy.

Fig. 2



Kaplan–Meier plot of 1-year survival free from episodes of congestive heart failure occurring at any time during the follow in the study patients divided according to the presence of history of hypertension.

found to be only marginally significant. However, of the possible risk factors, in our experience, hypertension was a strong predictor of CHF during subsequent trastuzumab administration, with a risk of CHF about three-fold higher in patients with hypertension than in those without. Our findings are in line with those reported by Braithwaite *et al.*[19], showing that hypertension was the most prevalent comorbidity among older breast cancer patients and does affect their mortality. Similarly, Jung *et al.*[20] found a close association between hypertension (considered alone or in a hypertension-augmented Charlson comorbidity score) and poor prognosis in women with metastatic breast cancer. In this study, a hypertension-augmented Charlson comorbidity score or hypertension *per se* were both strong independent predictors of the age–survival relationship among metastatic breast cancer patients, explaining the survival disparity between younger and older patients of 44 and 40%, respectively. Finally, Pinder *et al.*[21] reported that hypertension was an independent predictor of CHF with a hazard ratio of 1.45. These results provide clear evidence that hypertension hurts patients affected with malignancy.

Our study, indeed, is the first study demonstrating that in a middle-aged population with a large prevalence of patients without overt cardiac disease (only 2% had a history of coronary heart disease), hypertension emerged as the only prognostic factor for CHF.

How might hypertension contribute to the development of CHF? Abnormalities in proliferative pathways induced by hypertension-related breast cancer apoptosis can predispose to the growth of vascular smooth muscle cells, which often overdramatically respond to growth stimuli, with a final effect of shortening the cell cycle and increasing cellular proliferation[22,23]. Furthermore, hypertension may favor irregularities of carcinogen binding to deoxyribonucleic acid inducing breast cancer apoptosis through a genomic mechanism.[24] In addition, hypertension commonly generates large amounts of reactive oxygen species that may have cancer-promoting effects.[25]

A further consideration relates to the distribution of CHF events over time, which is not homogeneous (70% of events occurred within the first 6 months of trastuzumab therapy). This result is consistent with the Jones's multiple hit hypothesis, based on the concept that in the early stages of breast cancer, the cardiotoxic effects of aggressive anticancer pharmacological treatment makes cardiovascular adverse events more likely and the presence of risk factors, including hypertension, is results in a vicious circle of cardiovascular damage.[26] We should also note that myocardial cells of hypertensive women are particularly sensitive to trastuzumab damage after a first administration if given too soon following suspension of anthracycline therapy. It seems that anthracycline can interfere with the NRG/ErbB system in modulating myocardial response to injury;[27] makes cardiovascular events more likely and trastuzumab binding with ErbB2 receptors alters an important cardiac mechanism involved in the recovery from cardiac injuries due to stress factors.[28]

This is an important issue, highlighting the need for the clinician to be very careful over this period of trastuzumab therapy and to strictly follow these patients over this period of therapy when most of the symptoms of cardiotoxicity develop.

Conclusion

In clinical practice, new onset CHF seldom occurs in HER2-positive women with early breast cancer, and predominately in the first 6 months of therapy. CHF is invariably associated with a significant reduction in LVEF and is predicted by a history of hypertension. The main clinical implication of our study is to carefully follow these patients with a history of hypertension who should be considered at a higher risk for trastuzumab-induced CHF in the first period of treatment. Further researches are needed to assess whether the abovementioned risk is completely reversible on antihypertensive therapy, and whether risk reduction is linked with blood pressure lowering *per se*. While waiting for definite data from dedicated studies, hypertension should be always primarily considered in comorbidity information in breast cancer patients and taken into account in planning beneficial clinical strategies.

Acknowledgements

The members of the ICARO Network are as follows:

ICARO (ItalianCARdio – Oncological) Network: Participating Centers:

Aviano (IRCSS, Centro di Riferimento Oncologico): Chiara Lestuzzi;

Bari (IRCSS, Istituto Oncologico 'Giovanni Paolo II'): Stefano Oliva Agnese Maria Fioretti, Francesco Giotta, Agnese Latorre;

Belluno (Ospedale 'San Martino'): Luigi Tarantini, Paola Russo, Gaetano Sardina, Fausto Tuccia, Francesco Laveder;

Brescia (Spedali civili): Pompilio Faggiano, Marco Triggiani, Edda Simoncini;

Città di Castello (Ospedale civili): Donatella Severini;

Cremona (Azienda Ospedaliera 'Istituti Ospitalieri' di Cremona): Giuseppe Di Tano, Daniele Generali;

Fermo (Ospedale A Murri): Domenico Gabrielli, Lilliana Pennacchietti, Lucio Cardinali;

Napoli (IRCSS, Istituto Pascale): Nicola Maurea, Maria Crisitina Lombari, Michele De Laurentis, Carmen Pacilio;

Perugia (Ospedale S. M. della Misericordia): Stefania Gori, Gianfranco Alunni, Erberto Carluccio;

Roma (Ospedale San Camillo – Forlanini) Lidia Boccardi, Giovanni Pulignano;

Terni (Azienda Ospedaliera S. Maria). Daniella Bovelli, Paolo De Bonis, Martina Nunzi, Silvia Sabatini;

Trieste (Centro Cardiovascolare e Centro Sociale Oncologico-ASS1 Triestina): Giulia Russo, Andrea Di Lenarda, Rita Ceccherini.

There are no conflicts of interest.

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