

Enalapril and Carvedilol for Preventing Chemotherapy-Induced Left Ventricular Systolic Dysfunction in Patients With Malignant Hemopathies

The OVERCOME Trial (prevention of left ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive chemotherapy for the treatment of malignant hemopathies)

Xavier Bosch, MD, PhD,*† Montserrat Rovira, MD, PhD,†‡ Marta Sitges, MD, PhD,*† Ariadna Domènech, RN,‡ José T. Ortiz-Pérez, MD, PhD,*† Teresa M. de Caralt, MD, PhD,§ Manuel Morales-Ruiz, PhD,†|| Rosario J. Perea, MD, PhD,§ Mariano Monzó, MD, PhD,†¶ Jordi Esteve, MD, PhD†‡

Barcelona, Spain

Objectives	This study sought to evaluate the efficacy of enalapril and carvedilol to prevent chemotherapy-induced left ventricular systolic dysfunction (LVSD) in patients with hematological malignancies.
Background	Current chemotherapy may induce LVSD. Angiotensin-converting enzyme inhibitors and beta-blockers prevent LVSD in animal models of anthracycline-induced cardiomyopathy.
Methods	In this randomized, controlled study, 90 patients with recently diagnosed acute leukemia (n = 36) or patients with malignant hemopathies undergoing autologous hematopoietic stem cell transplantation (HSCT) (n = 54) and without LVSD were randomly assigned to a group receiving enalapril and carvedilol (n = 45) or to a control group (n = 45). Echocardiographic and cardiac magnetic resonance (CMR) imaging studies were performed before and at 6 months after randomization. The primary efficacy endpoint was the absolute change from baseline in LV ejection fraction (LVEF).
Results	The mean age of patients was 50 ± 13 years old, and 43% were women. At 6 months, LVEF did not change in the intervention group but significantly decreased in controls, resulting in a -3.1% absolute difference by echocardiography (p = 0.035) and -3.4% (p = 0.09) in the 59 patients who underwent CMR. The corresponding absolute difference (95% confidence interval [CI]) in LVEF was -6.38% (95% CI: -11.9 to -0.9) in patients with acute leukemia and -1.0% (95% CI: -4.5 to 2.5) in patients undergoing autologous HSCT (p = 0.08 for interaction between treatment effect and disease category). Compared to controls, patients in the intervention group had a lower incidence of the combined event of death or heart failure (6.7% vs. 22%, p = 0.036) and of death, heart failure, or a final LVEF <45% (6.7% vs. 24.4%, p = 0.02).
Conclusions	Combined treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with intensive chemotherapy. The clinical relevance of this strategy should be confirmed in larger studies. (Prevention of Left Ventricular Dysfunction During Chemotherapy [OVERCOME]; NCT01110824) (J Am Coll Cardiol 2013;61:2355-62) © 2013 by the American College of Cardiology Foundation

From the *Cardiology Department, Thorax Institute, Hospital Clinic, Barcelona, Spain; †Hematology Department, Hemato-Oncology Institute, Hospital Clinic, Barcelona, Spain; ‡Radiology Department, Hospital Clinic, Barcelona, Spain; §Human Anatomy Unit, Molecular Oncology and Embryology Laboratory, School of Medicine, Barcelona, Spain; ||Department of Biochemistry and Molecular Genetics, Hospital Clinic, Barcelona, Spain; and the ¶Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain.

This work was partially supported by Ministerio de Economía y Competitividad grant FIS EC07/90211 from the Instituto de Salud Carlos III, Madrid, Spain, and by the FEDER, European Union, Una manera de hacer Europa. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received November 5, 2012; revised manuscript received January 22, 2013, accepted February 6, 2013.

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin II receptor blocker

CMR = cardiac magnetic resonance

HSCT = hematopoietic stem-cell transplantation

LVEF = left ventricular ejection fraction

LVSD = left ventricular systolic dysfunction

PBSCT = peripheral blood hematopoietic stem-cell transplantation

SBP = systolic blood pressure

The prognosis of patients with hematological malignancies has improved because of the use of new chemotherapeutic and antineoplastic drugs and more dose-intensive regimens (1). Nonetheless, novel therapy has been associated with significant adverse events such as cardiac toxicity (2). In addition to anthracyclines, several other drugs used in the treatment plans of hematologic malignancies, either at standard doses during front-line therapy or as part of high-dose conditioning regimens for hematopoietic stem-cell transplantation (HSCT), may induce cardiac toxicity (2) through a

diversity of mechanisms including endothelial toxicity and direct myocyte injury (3–5). Even in asymptomatic patients, left ventricular systolic dysfunction (LVSD) might limit patients' treatment options and their long-term survival, because a significant proportion of them will relapse after front-line therapy and will require further salvage treatment, including HSCT in most instances (3).

See page 2363

Angiotensin-converting enzyme inhibitors (ACEI) have been demonstrated to slow the progression of LVSD and to prevent heart failure in asymptomatic high-risk patients (6) and to decrease mortality in post-infarction patients with LVSD and in patients with heart failure (6), including patients with anthracycline-induced cardiomyopathy (7). ACEI therapy has also been shown to have preventive effects against chemotherapy-induced cardiotoxicity in animal models (8,9) and in adult patients with early cardiotoxicity (10). Similar results have been obtained with the administration of beta-blockers in patients with post-infarction LVSD or heart failure (6), in animal models of cardiotoxicity (11,12) and in patients treated with anthracyclines (13,14). In addition, administration of both ACEI and beta-blockers has been shown to have additive beneficial effects in patients with LVSD (15) and is the recommended treatment in current guidelines (6).

Therefore, we designed the OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant hEmopathies) study to evaluate the effect of enalapril and carvedilol on the prevention of LVSD in patients with malignant hemopathies undergoing intensive chemotherapy (16).

Methods

Trial. This was a prevention, randomized, controlled trial performed at the Hospital Clinic of Barcelona, Spain. All patients were informed orally and in writing, and all gave their written consent before inclusion. The protocol was approved by the ethics committee of our institution, which recommended an open-label design of the study, considering the pilot nature of the trial, the severity of the treated diseases, the high incidence of infectious complications, and the potential hypotensive effect of the intervention. The study was conducted according to the Helsinki Declaration and registered with U.S. National Institutes of Health National Clinical Trials (NCT01110824).

Population of the study. Inclusion criteria were adult patients from 18 to 70 years old, in sinus rhythm and with normal echocardiographic LV ejection fraction ($LVEF \geq 50\%$), recently diagnosed with acute leukemia and referred for immediate intensive chemotherapy, and patients with relapsed or refractory Hodgkin and non-Hodgkin lymphoma and multiple myeloma undergoing autologous HSCT.

Exclusion criteria were the presence of congestive heart failure; $LVEF < 50\%$; prior myocardial infarction or documented coronary artery disease; significant valvulopathy or cardiomyopathy; renal failure (defined as an estimated glomerular filtration rate of < 30 ml/h/m²); hepatocellular insufficiency or grade III to IV increase of liver enzymes not secondary to tumoral liver infiltration; ongoing or expected need to be treated with ACEI, angiotensin II receptor blockers (ARB), or beta-blockers; prior allergy to ACEI or ARB; systolic blood pressure (SBP) lower than 90 mm Hg; asthma; atrioventricular block or sinus bradycardia (heart rate lower than 60 beats/min); persistent atrial fibrillation; need to be treated with a class I antiarrhythmic drug; pregnancy; and inability or unwillingness to give informed consent.

Randomization. Participants were randomly assigned in a 1:1 ratio to receive (the intervention group) or not to receive (the control group) enalapril and carvedilol. Randomization was centralized and performed by the hospital's Clinical Trials Unit, based on a series of random numbers generated by a computer program in blocks of random size and stratified by the patient cohort: acute leukemia versus other malignant hemopathies undergoing autologous HSCT.

Study treatment. Enalapril and carvedilol was started simultaneously at least 24 h before the first cycle of chemotherapy. The initial dose of enalapril was 2.5 mg twice daily (1.25 mg in patients with SBP between 90 mm Hg and 100 mm Hg) and was increased gradually every 3 to 6 days under close supervision to 5 mg and 10 mg twice daily if SBP persistently remained > 90 mm Hg and creatinine levels were < 2.5 mg/dl (or increased $< 25\%$ in patients with creatinine levels of > 1.3 mg/dl). In case of hypotension, the dose was reduced to the closest level or stopped, and the lowest dose was resumed when SBP persistently remained > 90 mm Hg.

The initial dose of carvedilol was 6.25 mg twice daily and increased gradually every 3 to 6 days to 12.5 mg and 25 mg twice daily in the absence of clinical signs of congestive heart failure, sinus bradycardia <60 beats/min or any degree of atrioventricular block. In the case of hypotension or bradycardia, the dose was also reduced to the closest level.

All patients received in-hospital chemotherapy according to the protocols of our institution (Online Table 1), and HSCT was performed using peripheral blood as stem cell source (PBSCT). The admission period was prolonged throughout the induction phase in patients with acute leukemia or the whole procedure in patients undergoing autologous PBHSCT until hematologic recovery, with a mean length of 30 days after inclusion in the trial. After completion of therapy, patients were followed in an outpatient clinic where enalapril and carvedilol were provided directly to the patients and they were evaluated at the end of the follow-up period, 6 months after randomization.

Endpoints. The primary outcome measure was the change from baseline in global LVEF, measured by echocardiography and by cardiac magnetic resonance (CMR) imaging, 6 months after randomization.

Secondary outcome measures included a predefined subgroup analysis of the results according to the patient cohort (acute leukemia vs. other malignant hemopathies) and to TnI and B-type natriuretic peptide (BNP) levels, the incidence of an absolute decrease in LVEF $\geq 10\%$ units associated with a decline below its normal limit of 50%; the incidence of death, heart failure, or significant LVSD as defined by an LVEF <45%; diastolic function, measured by Doppler echocardiography; and the incidence of severe life-threatening adverse events.

Six-month studies were performed when patients were in stable condition, otherwise, the study was delayed until the patient's recovery. All outcomes were assessed by independent investigators blinded to the patient's condition and allocated treatment. If suspected congestive heart failure occurred in any of the two arms during the study, a complete cardiac evaluation was performed, including a clinical echocardiographic study to confirm the diagnosis. If LV dysfunction was confirmed, the patients were considered to have achieved the endpoint of the study and were treated with ACEI and/or beta-blockers according to the treating physician's criteria.

Echocardiography. Echocardiographic-Doppler studies were performed with a commercially available system (Vivid 7; General Electric Medical System, Milwaukee, Wisconsin). Images were digitally stored for later off-line analysis with specific software (EchoPac, General Electric). LVEF was calculated using the Simpson method. Contrast-enhanced echocardiography was performed when the endocardial border visualization was not optimal. LV diastolic function was assessed in terms of LV inflow diastolic velocities, pulmonary vein flow, and lateral mitral annulus motion (17). Early (E) and late (A) peak diastolic velocities of LV inflow and the deceleration time (DT) of the E wave were determined by pulsed-wave Doppler, and the E/A ratio was

calculated. Pulmonary vein flow peak systolic (S) and diastolic (D) velocities were determined by pulsed-wave Doppler and the S/D ratio was calculated. The early peak diastolic velocity of the mitral annulus (Em) was determined using pulsed-wave Doppler tissue imaging, and the ratio E/Em was calculated as a surrogate for LV filling pressure. The left atrial area was also measured. All echocardiograms were interpreted blindly by a cardiologist unaware of the patient's condition and treatment.

Cardiac magnetic resonance imaging. CMR studies were carried out with a 1.5-T Sigma HD-x scanner (General Electric) under electrocardiographic gating conditions and using a cardiac phased-array surface coil. Global LV systolic function was assessed with a standard steady-state free precession cine sequence in sequential 10-mm thick short axis slices.

Identifying data were removed from CMR images for analysis. An experienced observer masked to patient treatment allocation and imaging point (baseline or end of the study) performed manual planimetry of the endocardial border at end-systolic and end-diastolic frames to compute LVEF, using commercially available software (Report card, General Electric).

TnI and BNP measurements. TnI was measured before, daily during each cycle of chemotherapy, and 12 and 24 h after each cycle. BNP concentrations were determined before and 12 h after each cycle of chemotherapy and following infusion of harvested HSCT. For each patient, only the highest TnI and BNP values were considered. Plasma levels of TnI were measured using a fluorometric enzyme immunoassay analyzer (Tn I-Ultra; Advia Centaur CP) with a functional sensitivity of 0.006 ng/ml and a cutoff level of 0.04 ng/ml corresponding to the 99th percentile of control values. BNP was measured using a chemiluminometric immunoassay run on the Advia Centaur Immunochemistry analyzer (Siemens Healthcare Diagnostics, Tarrytown, New York).

Sample size and statistical analysis. To detect an inter-group difference of 5 points in LVEF change from baseline to follow-up with a statistical power of 90%, a type I error risk of 5%, and an estimated SD of 6.5%, a total of 72 patients was estimated to be needed on the basis of a two-sided, two-sample Student *t* test. Assuming a 20% rate of incomplete measurements, a total of 90 patients was needed to be enrolled in the study.

All statistical analyses of the results were performed by the intention-to-treat method. Comparisons of baseline characteristics and incidence of clinical events between the intervention and control groups were performed with the unpaired Student *t* test, chi-square test, and Fischer exact test. BNP data were reported as medians (25th, 75th percentiles) and compared using the Mann-Whitney *U* test; the Spearman rank correlation test was used to correlate peak BNP levels and final LVEF. Differences between the two groups in terms of absolute changes in LVEF from baseline to 6 months after randomization were compared fitting mixed models for repeated measures with the (co)variance type set to unstructured. A sensitivity analysis was also conducted before

fitting the model by imputing a conservative value based on the 10th percentile of the overall response to those patients with missing values.

A pre-specified analysis included assessment of the primary outcome separately for patients with acute leukemia and for patients with lymphoma or multiple myeloma undergoing autologous PBSCT. The level of significance was set at the standard two-sided level of 5%. All analyses were performed using SAS version 9.1.3 software (SAS Institute Inc., Cary, North Carolina).

Results

Patients. From May 2008 to June 2010, 114 consecutive patients potentially eligible for the study were assessed, of whom 111 met inclusion criteria and 21 had some exclusion criteria. Forty-five of the resulting 90 patients were randomized to the intervention group and 45 to the control group (Fig. 1). The mean age of the patients was 50 ± 13 years of age, and 43% were women. Thirty-six patients had acute leukemia (of myeloid lineage in 30 and lymphoblastic in 6), and 54 had other malignancies undergoing PBSCT (9 with Hodgkin disease, 23 with non-Hodgkin lymphoma, and 22 with multiple myeloma).

The 2 groups were well balanced with respect to baseline characteristics and treatment received prior to and during the study, including anthracycline dose, except for the prevalence of smokers and of prior treatment with radiotherapy who were more frequent in the intervention group (Tables 1 and 2).

Study drugs. In the intervention group, the mean dose per patient per day of enalapril and carvedilol was 8.2 ± 5.9 mg

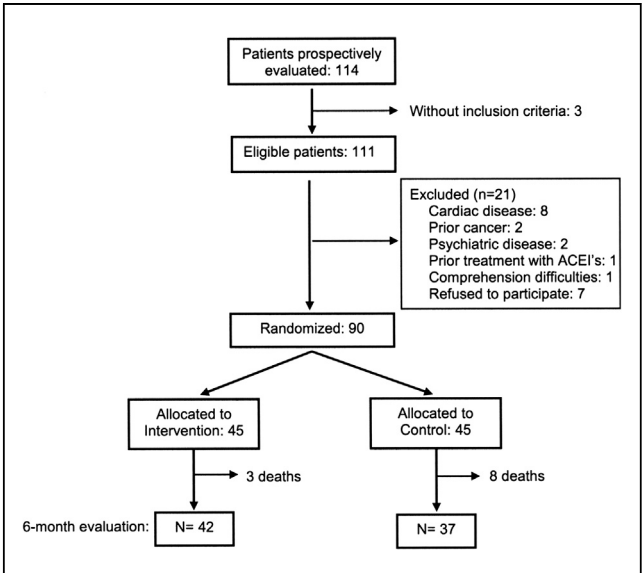


Figure 1 Flow Diagram of the OVERCOME Study

A total of 81% of all eligible patients during a 2-year period were enrolled in the study and were randomized to the intervention or control group. ACEI = angiotensin-converting enzyme inhibitor.

Table 1	Baseline Clinical Differences Between Groups		
	Intervention (n = 45)	Control (n = 45)	p Value
Age (yrs)	49.7 ± 13.9	50.9 ± 13.2	0.67
Women (%)	18 (40)	21 (47)	0.52
BSA (m ²)	1.86 ± 0.26	1.83 ± 0.21	0.62
Hypertension (%)	6 (13)	8 (18)	0.77
Hypercholesterolemia (%)	7 (16)	3 (7)	0.32
Statin treatment (%)	4 (9)	2 (4)	0.68
Diabetes (%)	3 (7)	1 (2)	0.62
Smokers (%)	13 (29)	4 (9)	0.03
Patient cohort (%)			1.00
Acute leukemia	18 (40)	18 (40)	
Autologous PBSCT	27 (60)	27 (60)	
SBP (mm Hg)	118 ± 17	118 ± 16	1.00
DBP (mm Hg)	73 ± 12	74 ± 10	0.66
HR (beats/min)	75 ± 12	78 ± 13	0.24
eCr _{cr} (ml/min)	105 ± 30	100 ± 30	0.30
Hemoglobin, g/l	107.8 ± 17	108 ± 20	0.97
Tnl (ng/ml)	0.013 ± 0.008	0.013 ± 0.010	0.80
BNP (ng/l)	19 (9, 38)	21 (12, 35)	0.88
LVEF (%)	62 ± 5.9	63 ± 5.9	0.50

Values are mean ± SD or n (%).
BNP = brain natriuretic peptide; BSA = body surface area; DBP = diastolic blood pressure; eCr_{cr} = estimated creatinine clearance rate by the Cockcroft-Gault formula; HR = heart rate; HSCT = hematopoietic stem cell transplantation; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure; Tnl = troponin I.

and 26.1 ± 18.2 mg, respectively, at 30 days, and 8.6 ± 5.9 mg and 23.8 ± 17 mg, respectively, at the end of the study. The maximum administered doses were 10.9 ± 5.9 mg/day for enalapril and 33.4 ± 16 mg/day for carvedilol.

Primary endpoint. Thirteen patients discontinued the study because of death in 11 patients and clinical heart failure in 2 patients. In those two patients, a final

Table 2	Anticancer Treatment Received by Patients Prior to and During the Study Period		
	Intervention (n = 45)	Control (n = 45)	p Value
Radiotherapy			
Prior (%)	6 (13)	2 (4)	0.27
During study (%)	6 (13)	2 (4)	0.27
Total (%)	12 (27)	4 (9)	0.05
Chemotherapy			
Prior (%)	27 (60)	27 (60)	1.00
No. of lines of therapy	1.4 ± 1.6	1.6 ± 1.9	0.47
During study	45 (100)	45 (100)	1.00
No. of cycles	1.73 ± 1.5	1.44 ± 0.8	0.27
Anthracyclines			
Prior (%)	19 (42)	17 (38)	0.67
Dose (mg/m ²)	151 ± 208	108 ± 150	0.26
During study (%)	18 (40)	18 (40)	1.00
Dose (mg/m ²)	139 ± 188	133 ± 182	0.87
Total (%)	37 (82)	35 (78)	
Dose (mg/m ²)	290 ± 189	241 ± 162	0.15
HSCT during study (%)	37 (82)	34 (78)	0.76

Values are n (%) or mean ± SD.
HSCT = hematopoietic stem cell transplantation.

Table 3	Differences in Change in LVEF Between the Intervention and Control Groups			
	Enalapril + Carvedilol	Control	Intergroup Difference	p Value
Echocardiography				
LVEF (%)	n = 42	n = 37		
Baseline	61.67 ± 5.11	62.59 ± 5.38		
6 months	-0.17 (-2.24 to 1.90)	-3.28 (-5.49 to -1.07)	-3.11 (-6.10 to -0.11)	0.04
CMR				
LVEF (%)	n = 31	n = 27		
Baseline	56.00 ± 6.00	60.18 ± 7.16		
6 months	0.36 (-2.41 to 3.13)	-3.04 (-6.01 to -0.07)	-3.40 (-7.43 to 0.63)	0.09

Values are mean ± SD or mean (95% confidence interval) 6-month change from baseline in absolute LVEF.
CMR = cardiomagnetic resonance imaging; LVEF = left ventricular ejection fraction.

echocardiographic study was obtained, resulting in 79 patients (88%) with complete echocardiographic data.

Echocardiographic LVEF was similar in the intervention and control groups at baseline. At 6 months, while no serial changes were observed in the intervention group, patients in the control group had a decrease in their mean LVEF that resulted in a global absolute intergroup difference of -3.11 points (p = 0.04) (Table 3).

Complete CMR studies could be obtained in only 58 patients (64%). Four patients refused to perform the baseline study and 28 did not perform the 6-month evaluation because of death in 11 patients, heart failure in 2 patients, and cancer progression and patient's refusal in 17 patients. Mean LVEF did not change in the intervention group but decreased by 3.04 absolute percentage points in the control group, resulting in a -3.40 absolute percentage intergroup difference (p = 0.09) (Table 3).

When a sensitive analysis was performed imputing the values of the 10th percentile to those patients with missing values, similar results were observed, with an estimated -3.61 (95% CI: -6.45 to -0.77) intergroup

absolute difference in echocardiographic LVEF (p = 0.013) and a -2.96 (95% CI: -6.08 to 0.16) difference in CMR LVEF (p = 0.063).

Secondary endpoints: disease category: acute leukemia versus autologous PBSCT. An interaction was observed in the echocardiographic LVEF results according to the disease category (p for interaction = 0.08), with more marked differences in patients treated for acute leukemia than in patients undergoing an autologous PBSCT. The mean intergroup difference in LVEF was of -6.38 (95% CI: -11.88 to -0.87, p = 0.025) absolute percent points in patients with acute leukemia (Fig. 2), and of -1.01 (95% CI: -4.46 to 2.45, p = 0.56) in patients with other malignancies undergoing PBSCT.

LV diastolic function. Baseline parameters of diastolic function were suggestive of normal to mild abnormal relaxation consistent with the mean age of the patients, with no left atrial enlargement, E/A ratio close to 1 and S/D ratio of pulmonary veins over 1. No significant changes in the diastolic parameters were observed in any of the groups at follow-up (Online Table 2).

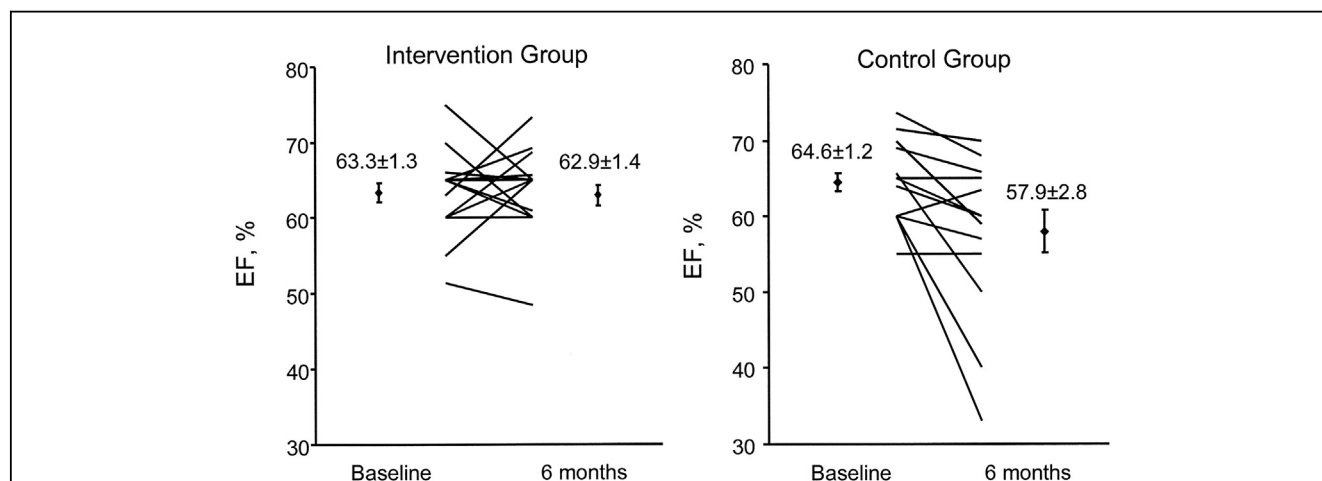


Figure 2 Change From Baseline in LVEF in Acute Leukemia Patients Undergoing Chemotherapy in the Intervention and Control Groups

While no differences were observed in the intervention group, patients in the control group had a 6.7% absolute decrease in their mean left ventricular ejection fraction (LVEF) (p = 0.025), with all but 3 patients having some degree of LVEF reduction. Values are mean ± SEM.

Biomarkers. Eleven patients (10 with acute leukemia and only 1 patient undergoing PBSCT, $p < 0.001$) experienced TnI elevation during chemotherapy: 7 in the intervention and 4 in the control group ($p = 0.52$). Nine of the 11 patients with positive troponin levels had TnI elevation at the end or early after a cycle of chemotherapy: 5 during the initial frontline therapy and 4 at 1 month later. Only 2 patients had troponin elevation both during initial treatment and 1 month later. The degree of TnI elevation was mild, and only 3 patients had TnI elevation over three times the upper reference limit. Recurring TnI elevation (≥ 2 episodes) occurred in 6 patients, with 3 patients in each study group. No interaction was found between the effects of enalapril and carvedilol on LVEF and TnI elevation ($p = 0.59$).

BNP elevation over 80 ng/l was common and occurred in 17 (47%) patients with acute leukemia and 24 (44%) patients undergoing HSCT, with no differences between the intervention and the control groups (53% versus 38%, $p = 0.14$). BNP elevation over 200 ng/l occurred in 7 and 2 patients, respectively ($p = 0.16$). No correlation was found between peak BNP levels and the change in LVEF ($R = -0.11$, $p = 0.34$).

Clinical endpoints. During the study period, 14 patients withdrew prematurely from the study because of death in 11 patients (cancer-related in 4 and infection-related in 7), heart failure in 2, and cancer progression in 1 patient. Five of 7 patients who died from an infectious cause were allocated to the control group. Patients who survived a septic episode during the trial experienced a mean decrease in final LVEF of 4.6 ± 9 absolute points, compared to a decrease of 0.6 ± 6 points in patients without sepsis ($p = 0.04$).

Compared to controls, the intervention group had a lower incidence of premature end of the study (6.7% vs. 24.4%, respectively, $p = 0.02$), of death or heart failure (6.7% vs. 22.2%, respectively, $p = 0.036$), and of the pre-specified secondary endpoint of death, heart failure or a final LVEF of $<45\%$ (6.7% vs. 24.4%, respectively, $p = 0.02$; Table 4). Patients treated with enalapril and carvedilol also showed a trend toward a lower incidence of heart failure or a $>10\%$ decrease in LVEF (9.5% vs. 19%, respectively, $p = 0.22$).

Safety. Globally, enalapril and carvedilol were well tolerated, although the dose of each drug had to be adjusted frequently according to the global patient status. During the first 30 days, enalapril was stopped in 3 patients, carvedilol

in 2, and both drugs in 1 patient, while transient discontinuation was indicated in 1, none, and 2 patients, respectively. New transient discontinuation frequency for the period of 1 to 6 months was indicated in 3, 2, and 3 patients, respectively.

Nine patients (20%) in the intervention group and 15 (33%) in the control group had life-threatening adverse events ($p = 0.15$) (Table 4). All of them were related to sepsis and required admission to an intensive care unit. None of the severe adverse effects that occurred in the intervention group were related to the treatment with enalapril and carvedilol.

Discussion

The OVERCOME study has shown that the concomitant treatment with enalapril and carvedilol may prevent LVSD in patients with malignant hemopathies treated with high-dose chemotherapy regimens. The results were consistent as measured with two-dimensional echocardiography or CMR, although the lower number of patients studied with the latter method precluded obtaining a conventional significant statistical difference. In addition, clinical events were less frequent in patients treated with the cardioprotective drugs. These results could have important clinical implications.

Comparison with other studies. Most studies of chemotherapy-induced cardiotoxicity have focused on the treatment of patients with heart failure or LVSD (2,7,18). In these patients, the current clinical practice is to stop chemotherapy and to restart it after LV recovery and to avoid further use of anthracyclines. However, even if LVSD improves after treatment, patients with chemotherapy-induced cardiotoxicity are prone to further deterioration in their LV function when confronted with further cycles of chemotherapy or even under stress conditions (19). Hence, in patients with cancer, the main objective should be to prevent rather than to treat cardiac toxicity (20).

ACEI have been shown to be effective against chemotherapy-induced cardiotoxicity in animal models (8,9). Although their use to prevent the progression of LVSD was disappointing in a study of pediatric cancer (18), a recent study reported favorable results when administered to adult patients with chemotherapy-induced

Table 4 Clinical Endpoints			
	Enalapril + Carvedilol	Control	p Value
Premature end of the study (%)	3 (6.7)	11 (24.4)	0.02
Total mortality (%)	3 (6.7)	8 (17.8)	0.11
Death or heart failure (%)	3 (6.7)	10 (22.2)	0.036
Death, heart failure or final LVEF<45% (%)	3 (6.7)	11 (24.4)	0.020
$\geq 10\%$ decrease in LVEF with a final LVEF<50% (%)	2 (4.8)	2 (5.4)	0.90
Heart failure or $\geq 10\%$ decrease in LVEF (%)	4 (9.5)	7 (19)	0.22
Severe adverse events* (%)	9 (20)	15 (33)	0.15

Values are n (%). *Defined as a serious adverse event that resulted in death or was life-threatening.
LVEF = left ventricular ejection fraction.

cardiac toxicity (10). Positive results have been also obtained with the administration of beta-blockers in animal models of chemotherapy-induced cardiomyopathy (11,12), and in two pilot studies of patients undergoing treatment with anthracyclines (13,14).

The magnitude of the results of our study was mild, with a 3.1% absolute difference in the mean LVEF between the intervention and control groups in the global population. Nevertheless, these results include very different individual responses and are in accordance with the results obtained in large clinical trials in which a 20% relative risk reduction is sought (6). Other studies have reported a higher effect of cardioprotection strategies. In the study performed by Cardinale et al. (10), 43% of the control and none of the enalapril group had a drop of more than 10% in LVEF, while heart failure occurred in 24% and 0%, respectively. Differences in the patient population, the intensity and type of chemotherapy, and the protocol design of both studies may explain these different results. Thus, the OVERCOME trial included patients with normal LVEF and normal troponin levels, whereas the study by Cardinale et al. (10) included only patients who experienced troponin elevation after high-dose chemotherapy, 44% of whom had persistent troponin elevation 1 month after randomization, representing a population with demonstrated chemotherapy-induced cardiotoxicity and at a much higher risk of chemotherapy-induced LVSD. In the study by Kalay et al. (13), in which low-dose carvedilol was administered, the patient population was markedly different: most patients were being treated for breast cancer, and all patients received high doses of anthracyclines.

Although, almost half of the patients presented elevated peak BNP levels, no intergroup differences were observed, and no correlation existed between LVEF reduction and BNP elevations. Many factors not directly related to cardiac toxicity might account for these findings, such as hyperhydration to prevent renal dysfunction and bladder toxicity during chemotherapy administration, repeated packed red cells and platelet transfusions, severe anemia, hypotension, acute kidney injury, or frequent infection episodes (21).

Effect on patients with acute leukemia. In our study, the effects were more pronounced in patients treated for recently diagnosed acute leukemia than for patients undergoing autologous PBSCT, with a mean 6.4% absolute difference in LVEF in the former group. Although this was a subgroup analysis, it was pre-specified in the study protocol and the randomization of the patients was stratified for this condition. In addition, an interaction was found between the effect of the intervention and the cohort of patients. These results are also in agreement with the type of the chemotherapy administered, which included several multiagent chemotherapy courses and repeated doses of anthracyclines in all patients of the acute leukemia group. On the contrary, patients allocated to the PBSCT cohort received only one chemotherapy course, the conditioning regimen, without anthracycline agents. Accordingly, the

number of patients with troponin elevation during treatment was much higher in the acute leukemia group, reflecting the higher cardiotoxic effect of the chemotherapy administered to these patients.

Diastolic function. Although we found significant changes in LVEF, an accepted measure of global LV systolic function, we did not find differences in LV indices of diastolic function. A recent study of carvedilol has reported similar results (14). The high variability of these measurements and their strong dependence on nonspecific and transient hemodynamic factors is a recognized limitation of these measurements. In addition, ACEI and beta-blockers have not been shown to be efficacious in patients with heart failure and preserved ejection fraction (6).

Effects on clinical events. The patients in the intervention group had a lower incidence of premature discontinuation of the study for any reason, of death or heart failure, and of death, heart failure, or significant LVSD. As two-thirds of all deaths were related to infectious complications in the context of post-chemotherapy neutropenia, it is difficult to elucidate whether enalapril and carvedilol could have influenced mortality. Considering that patients who survived septic complications experienced a significant reduction in their LVEF at the end of the study, when they were in a stable condition, and that LV function is a well-known determinant of survival in patients with sepsis (22), it could be speculated that the study intervention might have influenced mortality by impacting on the outcome of severe infectious episodes. Globally, these findings reinforce the importance of the results on LVEF.

Compliance and safety. Although drug dose titration had to be adjusted frequently according to the global patient's status, enalapril was stopped in only 3 patients, carvedilol in 2, and both drugs in only 1 patient. In addition, no differences were observed in the incidence of severe adverse effects between the intervention and control groups. Thus, the trial has proved that the combined administration of these drugs is safe in a setting of intensive therapy for high-risk diseases with a high myelotoxic potential and frequent development of infectious complications and hypotensive episodes.

Study limitations. The study was not blinded and placebo was not administered to the control group because of the pilot nature of the trial. However, the analyses of the imaging techniques were blinded, and the study was randomized and analyzed by the intention-to-treat method to minimize any possible bias. Complete CMR studies could only be obtained in 81% of the planned patients. Although statistical inference with missing data and sensitive analysis were applied, the CMR results lack enough statistical power to refuse a type II error. Also, the number of studied patients limits the value of the interaction found between the effect of the intervention on LVEF and the disease category. Finally, the administered doses of enalapril and of carvedilol were intermediate according to the patient's clinical condition. Larger doses could have obtained stronger effects. However, the doses used were determined by the patient's status and

safety, and similar to the doses used in large controlled trials performed in patients with heart failure (6).

Conclusions and clinical implications. This pilot randomized trial has proved that the combination of enalapril and carvedilol prevented LVEF reduction in patients with diverse hematological malignancies undergoing intensive chemotherapy. The results of the trial could have important clinical implications since each year millions of patients with cancer are treated with chemotherapy worldwide and are surviving the disease in greater numbers. Nonetheless, the clinical relevance of this strategy for prevention of chemotherapy-induced cardiac damage should be confirmed in larger future studies.

Reprint requests and correspondence: Dr. Xavier Bosch, Cardiology Department, Thorax Institute, Hospital Clinic, Villarroel 170, 08036 Barcelona, Spain. E-mail: xbosch@clinic.ub.es.

REFERENCES

1. Travis LB, Rabkin CS, Morris Brown L, et al. Cancer survivorship: genetic susceptibility and second primary cancers: research strategies and recommendations. *J Natl Cancer Inst* 2006;98:15–25.
2. Yeh ETH, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation* 2004;109:3122–31.
3. Schmitz N, Kloess M, Reiser M, et al. Four versus six courses of dose-escalated cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen plus etoposide (MegaCHOEP) and autologous stem cell transplantation: early dose intensity is crucial in treating younger patients with poor prognosis aggressive lymphoma. *Cancer* 2006;106:136–45.
4. Kuittinen T, Jantunen E, Vanninen E, et al. Cardiac effects within 3 months of BEAC high-dose therapy in non-Hodgkin's lymphoma patients undergoing autologous stem cell transplantation. *Eur J Haematol* 2006;77:120–7.
5. Chung T, Lim W-C, Sy R, Cunningham I, Trotman J, Kritharides L. Subacute cardiac toxicity following autologous haematopoietic stem cell transplantation in patients with normal cardiac function. *Heart* 2008;94:911–8.
6. Hunt SA, Abraham WT, Chin MH, et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2009;53:1343–82.
7. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy. Clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol* 2010;55:213–20.
8. Sacco G, Bigioni M, Evangelista S, Goso C, Manzini S, Maggi CA. Cardioprotective effects of zofenopril, a new angiotensin-converting enzyme inhibitor, on doxorubicin-induced cardiotoxicity in the rat. *Eur J Pharmacol* 2001;414:71–8.
9. Vaynblat M, Shah HR, Bhaskaran D, et al. Simultaneous angiotensin converting enzyme inhibition moderates ventricular dysfunction caused by doxorubicin. *Eur J Heart Fail* 2002;4:583–6.
10. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-risk chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006;114:2474–81.
11. Santos DL, Moreno AJ, Leino RL, Froberg MK, Wallace KB. Carvedilol protects against doxorubicin-induced mitochondrial cardiomyopathy. *Toxicol Appl Pharmacol* 2002;185:218–27.
12. Spallarossa P, Garibaldi S, Altieri P, et al. Carvedilol prevents doxorubicin-induced free radical release and apoptosis in cardiomyocytes in vitro. *J Mol Cell Cardiol* 2004;37:837–46.
13. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol* 2006;48:2258–62.
14. El-Shitany NA, Tolba OA, El-Shanshory MR, El-Hawary EE. Protective effect of carvedilol on adriamycin-induced left ventricular dysfunction in children with acute lymphoblastic leukemia. *J Card Fail* 2012;18:607–13.
15. Vantrimpont P, Rouleau JL, Wun CC, et al. Additive beneficial effects of beta-blockers to angiotensin-converting enzyme inhibitors in the Survival and Ventricular Enlargement (SAVE) Study. SAVE investigators. *J Am Coll Cardiol* 1997;29:229–36.
16. Bosch X, Esteve J, Sitges M, et al. Prevention of chemotherapy-induced left ventricular dysfunction with enalapril and carvedilol: rationale and design of the OVERCOME trial. *J Card Fail* 2011;17:643–8.
17. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;22:107–33.
18. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. *J Clin Oncol* 2004;22:820–8.
19. Huang C, Zhang X, Ramil JM, et al. Juvenile exposure to anthracyclines impairs cardiac progenitor cell function and vascularization resulting in greater susceptibility to stress-induced myocardial injury in adult mice. *Circulation* 2010;121:675–83.
20. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol* 2007;25:3991–4008.
21. Burjonrappa SC, Tong AT, Xiao LC, Johnson MM, Yusuf SW, Lenihan DJ. Cancer patients with markedly elevated B-type natriuretic peptide may not have volume overload. *Am J Clin Oncol* 2007;30:287–93.
22. Furian T, Aguiar C, Prado K, et al. Ventricular dysfunction and dilation in severe sepsis and septic shock: relation to endothelial function and mortality. *J Crit Care* 2012;27:319.e9–15.

Key Words: cardiac toxicity ■ carvedilol ■ chemotherapy ■ enalapril ■ left ventricular dysfunction ■ prevention.

APPENDIX

For supplemental tables, please see the online version of this article.