The Incremental Prognostic Value of Echocardiography in Asymptomatic Stage A Heart Failure

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Objective: This multicenter study consisted of echocardiographic examination of subjects with stage A heart failure (HF) with cardiovascular risk factors and normal electrocardiogram and clinical examination results to (a) define whether stage A subjects with risk factors are really free of functional or structural cardiac abnormalities and (b) assess the impact of the presence of risk factors and incremental value of echocardiographic parameters in the prediction of progression of HF or in the development of cardiovascular events.

Methods: A total of 1097 asymptomatic subjects underwent echocardiographic examination as a screening evaluation in the presence of cardiovascular risk factors. Left ventricular (LV) dysfunction, both systolic (ejection fraction) and diastolic (transmitral flow velocity pattern), was evaluated according to standard criteria. The subjects were divided according to different criteria: the presence of one or more risk factors, presence or absence of LV systolic dysfunction, and presence or absence of LV diastolic dysfunction. A follow-up period of 26 $\pm$ 11 months was performed, observing primary (cardiac death, myocardial infarction, coronary artery bypass grafting, percutaneous transluminal coronary angioplasty, acute pulmonary edema, stroke, and transient ischemic attack) and secondary (cardiologist-made diagnosis of HF and HF hospitalization) end points.

Results: The multivariate analysis for independent predictors of primary end points showed that age ($P = .001$), gender ($P = .02$), dyslipidemia ($P = .01$), obesity ($P = .001$), and systolic dysfunction ($P = .048$) represented the significant predictors. The multivariate logistic regression analysis for independent predictors of secondary end points showed that gender ($P = .02$), LV systolic dysfunction ($P = .01$), and LV diastolic dysfunction ($P < .01$) represented the significant predictors. The multivariate analysis for independent predictors of combined end points showed that only age ($P < .003$), gender (male: $P < .001$), obesity ($P < .04$), and systolic dysfunction ($P < .001$) represented the significant predictors. Echocardiography showed a high incremental value in the detection of systolic LV dysfunction and the prediction of cardiovascular events during follow-up in subjects with at least two risk factors.

Conclusion: This study demonstrated that preclinical functional or structural myocardial abnormalities could be detected by echocardiography in asymptomatic subjects with two or more cardiovascular risk factors and without electrocardiogram abnormalities (stage A of HF classification). The presence or absence of LV systolic dysfunction or LV diastolic dysfunction, as demonstrated by echocardiography, has an incremental value to cardiovascular risk factors in predicting both the evolution toward more severe HF stage C and the occurrence of cardiovascular events. (J Am Soc Echocardiogr 2010;23:1025-34.)

Keywords: Cardiovascular risk factors, Echocardiography, Heart failure

The prevalence of heart failure (HF) in the general population ranges between 0.4% and 2% and increases with age.[1,2] The presence of well-recognized, traditional risk factors for cardiovascular diseases (stage A) is sufficient to trigger a management response with the long-term goal of avoiding HF development. Patients in stage B are likewise ideal targets for HF prevention.[3] These individuals with

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Abbreviations

ASE = American Society of Echocardiography

CAD = Coronary artery disease

ECG = Electrocardiography

EF = Ejection fraction

HF = Heart failure

LV = Left ventricular

prevalent cardiovascular diseases but without overt symptomatic HF include the majority of patients whose hearts are undergoing progressive maladaptive cardiac remodeling, which leads to HF. These silent abnormalities may lead over time to symptomatic left ventricular (LV) dysfunction, but the progression can be positively influenced by early treatment.[4–6] Thus, early detection of subclinical LV dysfunction form is primary, with the aim of delaying HF evolution. However, most of the published studies on the epidemiology of HF include only symptomatic patients, and data on the prevalence of asymptomatic LV dysfunction in the general population are still lacking.[7,8] Echocardiography plays a pivotal role in the quantification and early detection of structural findings.[2-9]

The present study consisted of the echocardiographic examination of stage A subjects with one or more cardiovascular risk factors and a normal electrocardiographic and clinical examination to a) define whether stage A subjects with risk factors are free of functional or structural cardiac abnormalities and b) assess the impact of the presence of risk factors and the incremental value of echocardiographic parameters in the prediction of progression toward HF or in the development of other cardiovascular events in this population.

MATERIALS AND METHODS

Study Population

This is a multicenter study designed by the Italian Society of Cardiovascular Echography, the Disfunzione Asintomatica del Ventricolo Sinistro study, which included 1097 consecutive asymptomatic subjects (stage A) aged more than 18 years who were admitted to 19 echocardiographic laboratories for transthoracic examination as a screening evaluation in the presence of one or more cardiovascular risk factors. All laboratories were selected according to the operator's competence, level 3, in agreement with the American Society of Echocardiography (ASE) requirements.[10] The American College of Cardiology/American Heart Association guideline 2005 for HF identifies four stages of HF: stage A, at high risk for HF but without structural heart diseases or symptoms of HF; stage B, structural heart disease but without signs or symptoms of HF; stage C, structural heart disease with prior or current symptoms of HF; and stage D, refractory HF requiring specialized interventions.[11]

The study was approved by the local research ethic committees. The study enrolled subjects without a clinical history of HF or other cardiovascular diseases, according to inclusion criteria, with normal electrocardiography (ECG) tracings, and with normal clinical examination results in the presence of one or more cardiovascular risk factors. The definition of a normal ECG scan was according to *Marriott's Practical Electrocardiography* normality criteria.[12] All selected subjects underwent a complete two-dimensional echocardiographic study to evaluate LV functional and structural findings. Exclusion criteria were symptoms or clinical and instrumental signs of coronary artery disease (CAD), valvular heart disease (except mild forms not hemodynamically relevant), previous cardiac surgery or percutaneous coronary intervention, history of paroxysmal or persistent atrial fibrillation, anemia (hemoglobin < 12 mg/dL in women and < 13 mg/dL in men), renal failure (serum creatinine > 1.3 mg/dL), endocrinologic diseases (in particular, hypo- and hyperthyroidism, hyperaldosteronism). Pericardial disease, pulmonary hypertension, aortopathy, and cardiomyopathy were excluded on the basis of echocardiography.

All subjects provided written informed consent and detailed medical history, particularly on cardiovascular risk factors, comorbidities, and drug therapies. For study purposes, six cardiovascular risk factors were considered: hypertension (systolic blood pressure $\geq$ 140 mm Hg, diastolic blood pressure $\geq$ 90 mm Hg, or in drug treatment), diabetes mellitus (fasting glycemia $\geq$ 7.0 mmol/L^{-1} or in drug treatment), hypercholesterolemia (>200 mg/dL or in drug treatment), family history of cardiovascular disease (including CAD, cardiomyopathy, and other hereditary forms of cardiopathy), smoking ($\geq$1 cigarette/day, cessation of smoking $<$ 10 years previously was still considered as smoking), and obesity (body mass index $\geq$ 30 kg/m^2). We enrolled only prehypertensive (54%) or mild hypertensive (46%) asymptomatic subjects with normal ECG findings; on these terms, these patients were classified in class A.[13]

Diagnostic Criteria

All patients enrolled in the study underwent a physical examination, 12-lead electrocardiogram, and complete transthoracic echocardiographic examination, according to the standard protocol based on the ASE recommendations.[14] Anthropometric measurements (weight, height) were obtained, and body mass index was calculated (body weight in kilograms divided by height in meters squared). Blood pressure was measured twice at the right arm after a 10-minute rest in the supine position using a calibrated sphygmomanometer and then averaged. Echocardiograms were acceptable when at least 80% of the endocardium was visible. Quantitative analysis was done, for each laboratory, by the same expert operator. Measurements of LV ejection fraction (EF) were performed using the modified biplane Simpson's rule as a mean of three cardiac cycles. EF less than 50% was used as a cutoff for abnormal LVEF (LV dysfunction). LV diastolic function was evaluated according to the standard criteria.[9-15] The mitral flow was recorded in basal condition and during Valsalva maneuver.[9] The following diastolic parameters were assessed from the Doppler mitral flow and tissue velocities tracings: E-wave velocity, A-wave velocity, E/A, Δ E/A (changes from basal to Valsalva maneuvers), E-wave deceleration time, A-wave duration, E/e', and pulmonary venous flow (systolic velocity, diastolic velocity, *a* reverse wave duration). Diastolic function was classified according to recent recommendations of ASE on diastolic functional evaluation. The grading scheme was mild or grade I (impaired relaxation pattern), moderate or grade II (pseudonormalized filling), and severe (restrictive pattern) or grade III (Table 1). The majority of patients showed a normal diastolic filling pattern (58%), 32% of patients presented grade I diastolic dysfunction, and 10% of patients presented grade II diastolic dysfunction.[9-16] LV mass was calculated according to the Penn convention and indexed for height (g/$m^{2.7}$).[17] LV hypertrophy was defined as LV mass index $>$ 49.2 g/$m^{2.7}$ in men and $>$ 46.2 g/$m^{2.7}$ in women.[18] A random sample of 5% was centrally reanalyzed by two independent observers. The mean and standard deviation of variability between the two readings and by the same observer for the echocardiographic parameters were as follows: The intraobserver variability mean $\pm$ standard deviation values for EF were 64% $\pm$ 4% versus 66% $\pm$ 5% ($P < .06$), and the interobserver values were 62% $\pm$ 6% versus 67% $\pm$ 7% ($P < .07$). If the interobserver and intraobserver variability were considered in the identification of LV systolic or diastolic dysfunction, interobserver variability was 8.2% and

Table 1 Doppler criteria for classification of diastolic function

Normal diastolic function:	Mitral inflow:	0.75 < E/A > 1.5
	Deceleration time > 140 msec	
	Valsalva Maneuver:	Delta E/A < 0.5
	Doppler tissue imaging of mitral annular motion:	E/e' < 8
	Pulmonary venous flow:	S ≥ D
	Atrial reversal flow duration < A (mitral flow) duration (duration)	
Impaired relaxation (Grade I)	Mitral inflow:	E/A ≤ 0.75
	Deceleration time > 140 msec	
	Valsalva Maneuver:	Delta E/A < 0.5
	Doppler tissue imaging of mitral annular motion:	E/e' < 8
	Pulmonary venous flow:	S > D
	Atrial reversal flow duration < A (mitral flow) duration	
Pseudonormalization (Grade II)	Mitral inflow:	0.75 < E/A < 1.5
	Deceleration time > 140 msec	
	Valsalva Maneuver:	Delta E/A ≥ 0.5
	Doppler tissue imaging of mitral annular motion:	9 < E/e' < 15
	Pulmonary venous flow:	S < D
	Atrial reversal flow duration > A (mitral flow) duration + 30 msec	
Restrictive pattern (Grade III)	Mitral inflow:	E/A > 1.5
	Deceleration time < 140 msec	
	Valsalva Maneuver:	Delta E/A > 0.5
	Doppler tissue imaging of mitral annular motion:	E/e' > 15
	Pulmonary venous flow:	S < D
	Atrial reversal flow duration > A (mitral flow) duration + 30 msec	

intraobserver variability was 7.8% for systolic dysfunction, and interobserver variability was 8.7% and intraobserver variability was 7.5% for diastolic dysfunction.

Follow-Up and Outcome Events

All 19 echocardiographic laboratories involved in the study agreed to follow up the recruited patients. Thus, follow-up data were available for 905 subjects (82.4% of the initial sample) (mean duration 26 ± 11 months, range 16–60 months). Follow-up of patients was performed by using clinical controls (cardiologic visit), the hospital database, and phone contact to obtain information on clinical data and adverse events. The present study considered the following primary end points: cardiac death, myocardial infarction, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty, stroke, transient ischemic attack, and acute pulmonary edema. Secondary end points were (1) the HF hospitalization due to a clear change of normal clinical state of the patients (acute progression of HF stage) realized with a minimum of one night of hospitalization and involving at least two of the major Framingham criteria for the Clinical Diagnosis of Congestive Heart Failure;[19] and (2) cardiologist-made diagnosis of chronic progression of HF (HF stage C). For the diagnosis of myocardial infarction, stroke/transient ischemic attack, and acute pulmonary edema, standard laboratory, ECG, or examination criteria were used.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range, as appropriate. Categoric variables are presented as percentages and were compared using the chi-square test. Kruskal–Wallis one-way analysis of variance by ranks was used to examine differences of continuous variables among risk factor groups. The Mann–Whitney test was used to examine the difference of continuous variables between dichotomy variables. To identify predictive factors for occurrence of primary or secondary end points, we first performed three models of logistic regression analyses with cardiovascular risk factors and LV (systolic and diastolic) dysfunction as covariates, adjusting for age and gender, and with the outcomes mentioned above as dependent variables. Second, we calculated several survival curves using the Kaplan–Meier method for predicting primary or secondary end points according to cardiovascular risk factors (stratifying in three groups of subjects with one, two, or more cardiovascular risk factors), systolic function (normal or abnormal EF), and diastolic function (normal or abnormal). To establish the incremental value of echocardiography, we divided subjects with normal or abnormal systolic function according to the three groups of cardiovascular risk factors and tested the differences of primary end points, secondary end points, and combined, using the chi-square test. A two-tailed *P* value less than .05 was considered significant. All data were analyzed using SPSS software (version 13.0; SPSS, Inc., Chicago, IL).[20]

RESULTS

The demographic, epidemiologic, clinical, and echocardiographic variables are shown in Table 2. A total of 1097 subjects (median age 56 years, interquartile range 45–66 years, 569 men) formed the study population. In the selected population, hypertension was the most frequent cardiovascular risk factor, and diabetes mellitus was the least

Table 2 Sample characteristics

Family history n (%)	437 (39.8)
Current smokers n (%)	289 (26.3)
Diabetes n (%)	119 (10.8)
Hypertension n (%)	694 (63.3)
Dyslipidemia n (%)	389 (35.5)
Obesity n (%)	183 (16.7)
Male gender n (%)	569 (51.9)
Diuretics n (%)	158 (14.4)
ACE inhibitors n (%)	312 (28.4)
ARB n (%)	81 (7.4)
Calcium blockers n (%)	148 (13.5)
Beta-blockers n (%)	184 (16.8)
Alfa blockers n (%)	46 (4.2)
Aspirin n (%)	128 (11.7)
Statins n (%)	115 (10.5)
Age (y)	56 (45–66)
Weight (kg)	73 (63–83)
Height (cm)	167 (160–173)
BMI	26 (23.4–29)
HR (bpm)	70 (64–78)
SBP (mm Hg)	140 (125–150)
DBP (mm Hg)	80 (70–90)
EF (%)	61.7 (56.3–67.8)
Indexed LV mass ($g/m^{2.7}$)	38.4 (30.4–46.5)
LV end-diastolic diameter (mm)	49 (46–53)
LV end-systolic diameter (mm)	30 (28–34)
LA diameter (mm)	37 (32–41)
LA area (cm^2)	16 (14–19)

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *BMI*, body mass index; *HR*, heart rate; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *EF*, ejection fraction; *LV*, left ventricular; *LA*, left atrial.

frequent risk factor. Angiotensin-converting enzyme inhibitors were the most used drug (28.4%), and beta-blockers were used by only 16.8% of the studied population.

A total of 905 subjects (82.4%) were observed in the follow-up (mean time: 26 months ± 11) and divided into three subgroups according to the number of cardiovascular risk factors: group I, 355 subjects (39.2%) with one cardiovascular risk factor, median age 54 years, interquartile range 40 to 65 years, 184 were male; group II, 312 subjects with two cardiovascular risk factors, median age 58 years, interquartile range 51 to 67 years, 153 were male; group III, 238 subjects with three or more cardiovascular risk factors, median age 57 years, interquartile range 50 to 65.2 years, 139 were male.

The prevalence of LV systolic and diastolic dysfunction in these three groups is shown in Figure 1. LV systolic dysfunction is significantly different among the groups ($P<.018$), whereas LV diastolic dysfunction is not.

Follow-up

During the follow-up period, 38 primary end points (3.3%) were observed; secondary end points were observed in 47 subjects (5.2%). The details of their distribution are shown in Table 3. Univariate analysis of possible predictors of primary, secondary, or combined end points is shown in Table 4. Primary end points are related to gender ($P<.002$) and age ($P<.001$). Diabetes, obesity, and dyslipidemia are the more important risk factors in predicting primary end points. From a structural point of view, LV mass and LV systolic and diastolic volumes, indexed to height, are significant predictors of primary end points (Table 5). The multivariate analysis for independent predictors of cardiovascular primary end points showed that age ($P=.001$), gender ($P=.02$), dyslipidemia ($P=.01$), obesity ($P=.001$), and systolic dysfunction ($P=.048$) represented the significant predictors (Table 5). The multivariate logistic regression analysis for independent predictors of secondary end points showed that gender ($P=.02$), LV systolic dysfunction ($P=.01$), and LV diastolic dysfunction ($P<.01$) represented the significant predictors (Table 6). The multivariate analysis for independent predictors of combined end points showed that only age ($P<.003$), gender (male: $P<.001$), obesity ($P<.04$), and systolic dysfunction ($P<.001$) represented the significant predictors (Table 7).

Kaplan–Meier cumulative survival curves for subjects divided into three groups according to risk factors for predicting primary end points showed a significant difference in the incidence of events in the third group ($P=.001$) (Figure 2A), whereas cumulative survival curves for subjects divided according to EF $>$ 50% and $\leq$ 50% showed a significant increase of events in subjects with LV systolic dysfunction ($P=.009$) (Figure 2B).

Kaplan–Meier cumulative survival curves for subjects divided into three groups according to risk factors for predicting secondary end points showed a significant progression to overt HF in the three groups ($P=.024$) (Figure 3A), whereas cumulative survival curves for subjects divided according to EF $>$ 50% and $\leq$ 50% showed a significant increase of events in subjects with LV systolic dysfunction ($P=.001$) (Figure 3B). If subjects were divided according to the presence or absence of diastolic dysfunction, we observed a significant increase of events in subjects with LV diastolic dysfunction ($P<.001$) (Figure 3C). Kaplan–Meier cumulative survival curves for subjects divided into three groups according to risk factors for predicting combined end points confirmed that group III will significantly develop more events (Figure 4A).

If we consider the risk factors in the three groups, the presence or absence of systolic dysfunction detected by echocardiography showed an incremental value in predicting primary end points only for group III ($P<.001$) (Figure 5A), whereas for secondary and combined end points the previous observation is extended also to group II (Figure 5B, C).

DISCUSSION

The main findings of our study are as follows:

1. In the group of asymptomatic subjects with stage A HF, defined on the basis of history, physical examination, and normal ECG, echocardiography allowed the identification of a relevant percentage of subjects with functional and structural LV abnormalities (both systolic and diastolic dysfunction) (stage B).
2. Cardiovascular risk factors, according to other studies, predicted cardiovascular events that occurred during the follow-up, essentially when two or more of them coexisted.
3. The high value of LV dysfunction detection by echocardiography enabled the prediction of cardiovascular events during follow-up in subjects with at least 2 risk factors.
4. Echocardiographic parameters of both systolic and diastolic function identified the progression toward overt HF, in comparison with cardiovascular risk factors, which were unable to do so.

According to the recent scientific statement on Prevention of Heart Failure from the American Heart Association Councils on Epidemiology and Prevention,[21] which recommends appropriate studies (still lacking) to identify and treat asymptomatic individuals

Number or risk factors (groups)	1	2	>=3	P=
LVSD n (%)	29 (8.2)	29 (9.3)	36 (15.1)	0.018
LVDD n (%)	97.0(32)	101 (38.1)	79 (38.3)	0.213

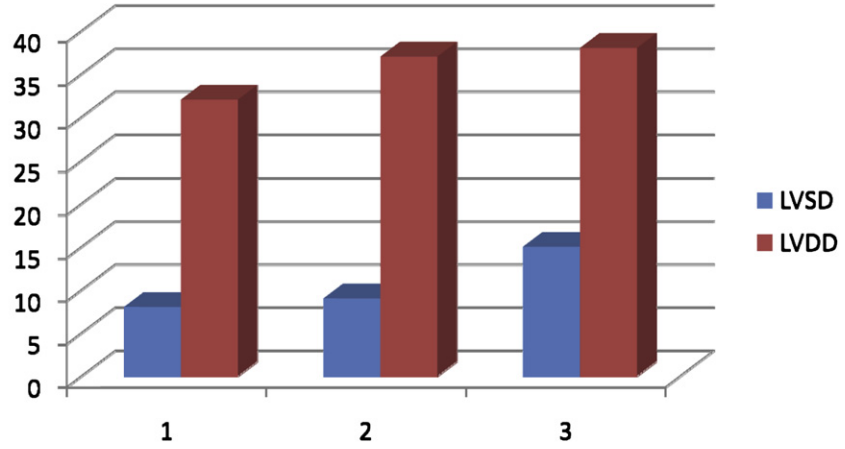

Figure 1 Prevalence of LV systolic and diastolic dysfunction according to the number of risk factor groups. *LVSD*, Left ventricular systolic dysfunction; *LVDD*, left ventricular diastolic dysfunction.

with LV dysfunction (stage B) and to prevent its development, the Italian Society of Cardiovascular Echography planned a multicenter perspective study on asymptomatic LV systolic dysfunction to analyze its prevalence and the role of echocardiography in the diagnostic and prognostic strategy in subjects with stage A HF with risk of developing cardiac remodeling.

With the increasing focus on addressing stage A HF as the best means of preventing the final common pathway of overt HF (stages C and D), attention needs to be directed toward screening for hypertension, diabetes mellitus and dyslipidemia, smoking, gender, and age. Prospective epidemiologic studies have identified risk factors and risk markers for HF development (stage A).

The identification of individuals who are at risk for HF is potentially useful for the implementation of HF-prevention strategies. It is not yet clear whether all stage A subjects or only those at high risk of developing HF should be screened using serial noninvasive assessment for the advent of ventricular dysfunction (stage B). The present study affirms that only echocardiography can differentiate between stage A (presence of risks factors without LV systolic and diastolic dysfunction) and stage B, with the evidence of some functional or structural myocardial abnormalities. On the other hand, other imaging modalities can also differentiate between stage A and B, such as a Holter ECG or magnetic resonance imaging scan.

Data from randomized trials showed a different prevalence of asymptomatic LV dysfunction, in relation to the different study groups, different methods used in the evaluation of LV function, and a different LVEF cutoff value to define asymptomatic LV dysfunction. Thus, the prevalence of asymptomatic systolic LV dysfunction in the general population is still uncertain.[22]

In a recent community-based study, the prevalence of preclinical LV systolic dysfunction was 6% in the overall population and 13.7% in patients older than 65 years and with hypertension or CAD.[9] Other studies have confirmed a relatively high prevalence of this condition, using a reduction in LVEF or fractional shortening as an echocardiographic marker of LV dysfunction.[23-26] In addition, few data are available on the prevalence of asymptomatic diastolic LV dysfunction. Redfield and colleagues[9] evaluated the prevalence of asymptomatic diastolic LV dysfunction and reported a value of 27.4% in the overall population, which increased to 64.1% in patients aged more than 65 years with hypertension or CAD.

Table 3 Description of end points

Description of outcomes	N (%)
Primary end points	
Cardiac death	3 (0.3)
Myocardial infarction	6 (0.7)
Stroke or TIA	3 (0.3)
CABG or PTCA	17 (1.9)
Acute pulmonary edema	9 (1)
Secondary end points	
Cardiologist made diagnosis	17 (1.9)
Heart failure hospitalization	30 (3.3)

Time of follow-up (mean ± SD): 26 ± 11 months.
TIA, Transient ischemic attack; *CABG*, coronary artery bypass grafting; *PTCA*, percutaneous transluminal coronary angioplasty; *SD*, standard deviation.

In the present study, LV mass and left atrium enlargement were not predictive of outcome, whereas a recent study by Stevens *et al.*[27] showed them to be markers of higher risk. These two parameters, as is well known, were altered essentially by a hypertensive state; therefore, a possible explanation of this apparent discrepancy could be due to different selected study populations. Our sample consisted of asymptomatic patients without ECG abnormalities, and in particular the group of hypertensive subjects (63%) were classified as prehypertensive (54%) and mild hypertensive (46%), whereas Stevens and colleagues' study population consisted of outpatients with CAD (71% hypertensive) with a higher range of systolic and diastolic blood pressure, if compared with our population study.

Table 4 Univariate analysis of possible predictors of primary or secondary end points or combined

		Secondary end points		Primary end points		Combined	
	Overall	n (%) or median, IQR	*P* <	n (%) or median, IQR	*P* <	n (%) or median, IQR	*P* <
Male	476	35 (7.4)	.003	27 (5.7)	.002	52 (10.9)	.000
Diabetes	111	11 (9.9)	.020	10 (9)	.002	17 (15.3)	.001
Hypertension	583	36 (6.2)	.078	21 (3.6)	.924	46 (7.9)	.353
Current smokers	236	12 (5.1)	.930	8 (3.4)	.807	17 (7.2)	.951
Dyslipidemia	315	22 (7)	.079	21 (6.7)	.001	33 (10.5)	.008
Obesity	167	13 (7.8)	.099	15 (9)	.000	20 (12)	.011
Family history of CAD	360	17 (4.7)	.604	13 (3.6)	.963	25 (6.9)	.743
1 risk factor	355	11 (3.1)	.048	6 (1.7)	.001	15 (4.2)	.005
2 risk factors	312	18 (5.8)		9 (2.9)		24 (7.7)	
≥3 risk factors	238	18 (7.6)		18 (7.6)		27 (11.3)	
Diastolic dysfunction	277	16 (8.1)	.028	7 (3.6)	.847	20 (10.2)	.074
Systolic dysfunction	94	17 (18.1)	.000	8 (8.5)	.011	18 (19.1)	.000
Age (y)	57 (46–65)	59 (52–65)	.001	68 (64–69)	.000	61 (53–68)	.000
BMI	25 (23–28)	26 (24–30)	.015	30 (25–32)	.002	26 (24–31)	.005
SBP (mm Hg)	140 (125–150)	140 (130–150)	.611	135 (130–140)	.405	140 (130–146)	.867
DBP (mm Hg)	80 (80–90)	80 (75–90)	.119	80 (70–80)	.002	80 (74–90)	.016
EF (%)	64 (58–69)	49 (45–59)	.001	49 (42–75)	.209	49 (44–60)	.060
LVM_{bsa}	93 (77–113)	124 (107–148)	.000	134 (91–156)	.022	120 (101–149)	.000
LVM_h	43 (35–52)	56 (53–66)	.000	61 (41–77)	.013	55 (43–67)	.000
EDV (mL)	93 (71–117)	107 (92–144)	.000	126 (69–141)	.002	111 (92–141)	.000
ESV (mL)	32 (23–45)	57 (42–74)	.000	49 (28–75)	.009	57 (33–74)	.000
LVDD (mm)	50 (46–53)	53 (50–55)	.000	51 (48–54)	.007	52 (49–55)	.000
LVSD (mm)	30 (28–34)	36 (30–42)	.000	29 (23–40)	.036	35 (29–40)	.000
LA diameter (mm)	37 (33–41)	41 (37–46)	.000	40 (34–44)	.062	41 (36–44)	.000

BMI, Body mass index; *SBP,* systolic blood pressure; *DBP,* diastolic blood pressure; *EF,* ejection fraction; LVM_{bsa}, left ventricular mass indexed by body surface area; $LVM_h^{2.7}$, left ventricular mass indexed by height$^{2.7}$; *EDV,* end-diastolic volume; *ESV,* end-systolic volume; *LVDD,* left ventricular internal diameter; *LVSD,* left ventricular systolic diameter; *LA,* left atrium; *IQR,* interquartile range; *CAD,* coronary artery disease.

Table 5 Predictive value of cardiovascular risk factors and left ventricular function: Logistic regression analysis

	OR (CI 95%)	*P*
Age	1.08 (1.03–1.13)	.001
Diabetes	1.46 (0.55–3.86)	.44
Hypertension	0.54 (0.21–1.34)	.18
Current smokers	1.49 (0.50–4.42)	.47
Dyslipidemia	3.08 (1.29–7.37)	.01
Obesity	4.18 (1.72–10.14)	.001
Family history	1.08 (0.45–2.58)	.86
Male	3.22 (1.21–8.57)	.02
LVSD	2.77 (1.01–7.61)	.05
LVDD	0.72 (0.29–1.78)	.48

OR, Odds ratio; *CI,* confidence interval; *LVSD,* left ventricular systolic dysfunction; *LVDD,* left ventricular diastolic dysfunction.
Dependent variable: primary end points (LVSD and LVDD).

Table 6 Predictive value of cardiovascular risk factors and left ventricular function: Logistic regression analysis

Age	1.03 (1.00–1.07)	.07
Diabetes	1.57 (0.68–3.60)	.29
Hypertension	1.26 (0.53–3.00)	.60
Current smokers	0.89 (0.36–2.18)	.80
Dyslipidemia	1.26 (0.62–2.59)	.52
Obesity	1.48 (0.64–3.42)	.35
Family history	0.90 (0.42–1.91)	.78
Male	2.56 (1.13–5.77)	.02
LVSD	5.75 (2.65–12.49)	.001
LVDD	2.59 (1.20–5.57)	.01

LVSD, Left ventricular systolic dysfunction; *LVDD,* left ventricular diastolic dysfunction.
Dependent variable: secondary end points (LVSD and LVDD).

Possible Strategies of Screening for Asymptomatic Left Ventricular Systolic Dysfunction

Three possible strategies to select patients to undergo ultrasound examination have been proposed: electrocardiogram, natriuretic peptide levels, and a composite clinical score.[22] The performance of the surface electrocardiogram as an initial screening tool for systolic LV dysfunction has been examined in several investigations.[28] Some reports have suggested that ECG has a high sensitivity and negative predictive value, and a low positive predictive value.[29] A clinical score based on high-risk characteristics has been used in the Framingham Heart Study with fair accuracy for identifying systolic LV dysfunction.[30] Natriuretic peptides have emerged as an attractive tool for screening because plasma levels are elevated in systolic LV dysfunction, are relatively cardiac specific, and can be assayed rapidly.[31,32] However, all these approaches cannot characterize the

Table 7 Predictive value of cardiovascular risk factors and left ventricular function: Logistic regression analysis

	OR (CI 95%)	*P*
Age	1.05 (1.01–1.08)	.003
Diabetes	1.56 (0.77–3.19)	.22
Hypertension	0.82 (0.42–1.62)	.57
Current smokers	1.13 (0.53–2.40)	.75
Dyslipidemia	1.63 (0.89–3.00)	.11
Obesity	2.03 (1.02–4.04)	.04
Family history	0.99 (0.53–1.86)	.98
Male	3.39 (1.65–6.94)	.001
LVSD	3.59 (1.76–7.30)	<.001
LVDD	1.69 (0.90–3.18)	.10

OR, Odds ratio; *CI*, confidence interval; *LVSD*, left ventricular systolic dysfunction; *LVDD*, left ventricular diastolic dysfunction.
Dependent variable: combined end points (LVSD and LVDD).

type and severity of structural and functional cardiac alterations as echocardiographic technique.

Our study followed the integrated clinical (history, presence or absence of cardiovascular risk factors), ECG, and echocardiographic approach. Subjects with any electrocardiographic abnormalities were assessed to evaluate the pure diagnostic and prognostic power. On the other hand, if we considered the 2007 American College of Cardiology/American Heart Association/ASE Appropriateness Criteria for Transthoracic and Transesophageal Echocardiography,[33] echocardiography in asymptomatic subjects with normal ECG results and cardiovascular risk factors was considered inappropriate as a screening method and essentially too expensive. An effective screening program ideally should identify those patients likely to have asymptomatic LV dysfunction by using an inexpensive questionnaire, a risk profile, or a blood test, which could then be confirmed by echocardiography. Our study demonstrated that in patients with multiple cardiovascular risk factors, echocardiography is relevant to identify subjects with asymptomatic LV dysfunction, exclude any significant functional and structural heart involvement, and select patients who might develop cardiovascular disease, going by HF hospitalization to cardiac death.

Echocardiography and Heart Failure Development

Multiple morphologic and physiologic measures obtained by echocardiographic and magnetic resonance imaging identify individuals at higher risk of developing HF. Ventricular dilatation, represented by an increase in end-diastolic or end-systolic dimensions,[22] increased LV mass,[34,35] and evidence of LV diastolic filling impairment, and asymptomatic systolic dysfunction[8] are associated with an increased likelihood of overt HF.

Our results demonstrated that in stage A, in the presence of a single risk factor, both systolic (8.5%) and diastolic (32.5%) dysfunction are present. The increased number of risk factors determines a significant increase in the prevalence of systolic dysfunction.

The definition of asymptomatic LV dysfunction relies on the identification of functional or structural cardiac abnormalities that may herald the development of HF symptoms and subsequent cardiac events, as recently supported by a community study that showed a 4.7-fold increased risk of HF at 12-year follow-up in patients with asymptomatic systolic LV dysfunction.[8] In addition, isolated diastolic LV dysfunction may also occur and progress to HF with preserved LV systolic function.

Echocardiography is a powerful tool that can clearly identify early structural and functional cardiac changes in patients who will develop clinical signs and symptoms of HF. Consequently, it has been used as the standard criterion for LV dysfunction diagnosis in community-based studies and most clinical trials.[22] Although echocardiographically derived LVEF and diastolic parameters can be influenced by preload and afterload changes, these indices are widely used for the evaluation of systolic and diastolic (dys)function.

Cardiac remodeling, detected by echocardiography, occurs in a significant percentage of subjects in our study. In particular, LV mass and LV volumes are significant univariate predictors of primary and secondary end points. Asymptomatic LV dysfunction predicts both primary and overall end points, whereas diastolic dysfunction predicts only a secondary end point (HF hospitalization).

In our follow-up data, the coexistence of two or more cardiovascular risk factors is able to predict both primary and secondary end points. The prediction of both primary end points and all events is best achieved by the echocardiographic detection of LV systolic dysfunction. The LV diastolic dysfunction could be useful in predicting the progression of HF stage.

The echocardiographic examination is able to detect, also in stage A subjects without ECG abnormalities, the presence of asymptomatic LV dysfunction, which has a significant incremental value in the prediction of cardiovascular events. This finding is particularly evident in subjects with at least three cardiovascular risk factors for predicting cardiovascular events. For secondary end points, the echocardiography detection of asymptomatic LV dysfunction also has incremental value in subjects with two or more risk factors.

On the other hand, we can affirm that only echocardiography can identify subjects with stage A HF, differentiating them from those with stage B HF; for this reason, we agree with a new proposal to revise the classification of cardiomyopathy in which stage 1 (latent or potential) is defined as "when a factor known to be associated with cardiomyopathy is present (genetic abnormality, diabetes mellitus, etc.), but no evidence of heart muscle disease can be detected even with sensitive noninvasive techniques."[36] This concept was revisited and expanded by Sengupta and Narula,[37] in the light of new echocardiography technologies, confirming that in stage 1 (subjects at risk of cardiomyopathy or HF) normal subendocardial and subepicardial function can be detected by echocardiography.

STUDY LIMITATIONS

A study limitation was the use of composite outcomes, selecting primary end points more related to atherosclerosis and not necessarily to HF, except acute pulmonary edema.

The use of standard echocardiography methods and not more sophisticated methods (e.g., strain imaging) could be considered both a limitation and a strength of the study. The limitation is that strain imaging will prove to be more sensitive for detecting subclinical abnormalities of both systolic and diastolic function, and the strength is that the present study was focused on the utility of currently established and widely available echocardiographic techniques. Strain imaging may prove to be better, but it is not used widely enough to serve as a screening tool.

Another limitation is that not all patients completed follow-up, and this information is not available to make meaningful comparisons between those who did and did not complete follow-up, to establish the differences.

The low prevalence of adverse events described in the present study, because of the study population size and length of follow-up,

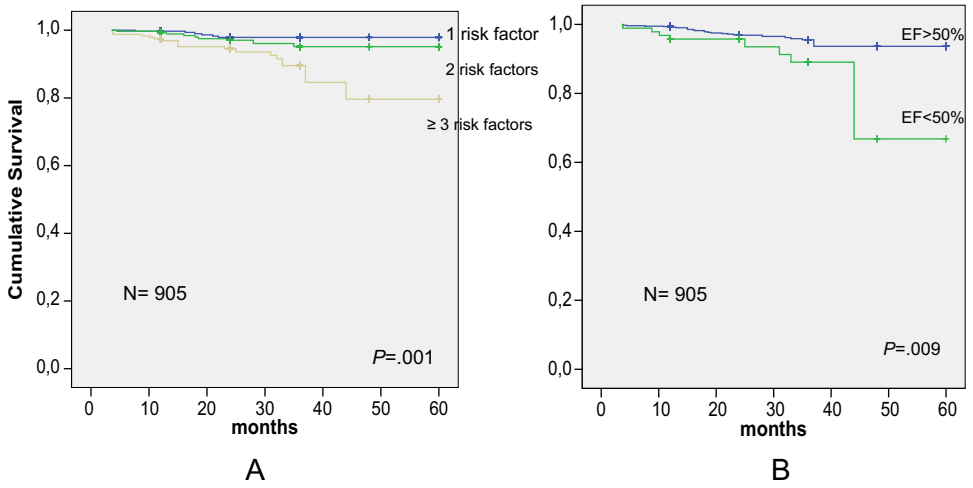

Figure 2 Kaplan–Meier curves for predicting primary end points in subjects with one or more cardiovascular risk factors **(A)** and with normal or abnormal LVEF **(B)**. *EF,* Ejection fraction.

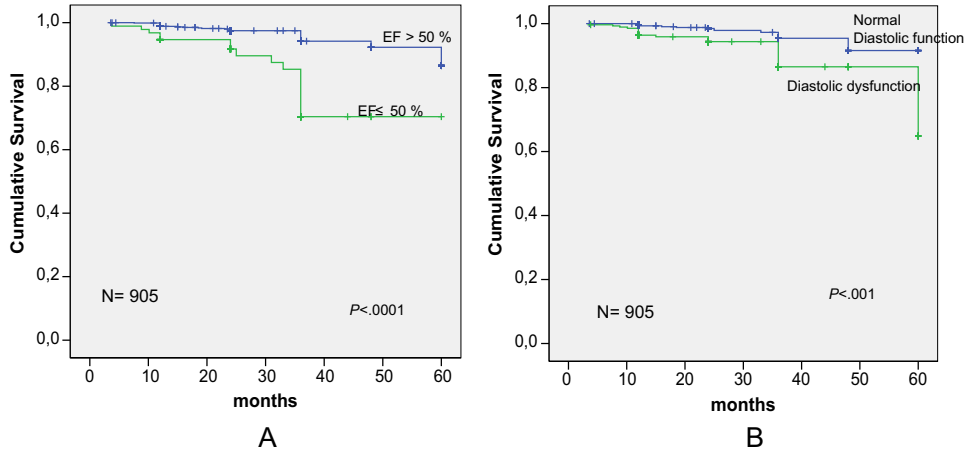

Figure 3 Kaplan–Meier curves for secondary end points in subjects with normal or abnormal LVEF **(A)** and with normal or abnormal diastolic function **(B)**. *EF,* Ejection fraction.

could be considered another limitation of study, whereas this may not be surprising in a group of patients with pre-clinical HF.

Another limitation of the study is represented by the lack of determination of natriuretic peptide (B-type natriuretic peptide and pro-B-type natriuretic peptide) levels. A recent work demonstrated that increased concentrations of both these biochemical markers can accurately detect asymptomatic LV systolic dysfunction.[38]

CONCLUSIONS

Asymptomatic LV systolic dysfunction, as a precursor to HF and cardiovascular death, is an important contemporary health problem. This study demonstrated that in subjects with two or more cardiovascular risk factors and without ECG abnormalities (stage A of HF classification), echocardiography could detect preclinical functional or structural myocardial abnormalities. The presence or absence of LV systolic or diastolic dysfunction, as demonstrated by echocardiography, has an incremental value to cardiovascular risk factors in predicting both the evolution toward a more severe HF stage (C) and the occurrence of cardiovascular events.

This message could be important in the current cost-conscious climate, in which a higher awareness of the relevance of appropriate use of imaging modalities is emerging. Although not validated, a potential screening strategy is the measurement of plasma B-type natriuretic peptide in a high-risk population, followed by echocardiography in those patients with elevated B-type natriuretic peptide.

In subjects with two or more cardiovascular risk factors, the routine use of conventional echocardiography is strongly recommended to identify subjects with asymptomatic LV systolic dysfunction. These subjects should be carefully observed from a clinical point of view and eventually managed more aggressively, including a more restricted diet, lifestyle modifications, and, when necessary, a more comprehensive pharmacologic approach, in the attempt to correct the modifiable cardiovascular components and consequently delay the occurrence of overt HF.

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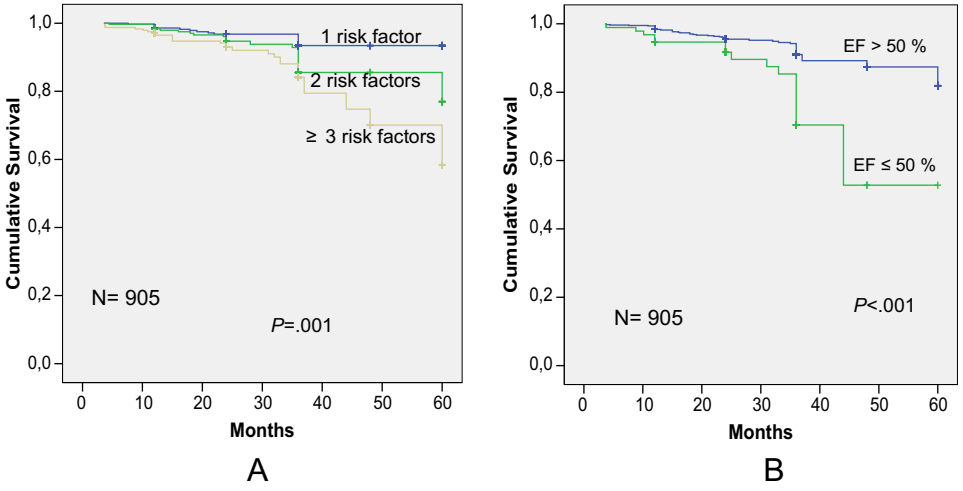

Figure 4 Kaplan–Meier curves for predicting combined end points in subjects with one or more cardiovascular risk factors **(A)** and with normal or abnormal LVEF **(B)**. *EF*, Ejection fraction.

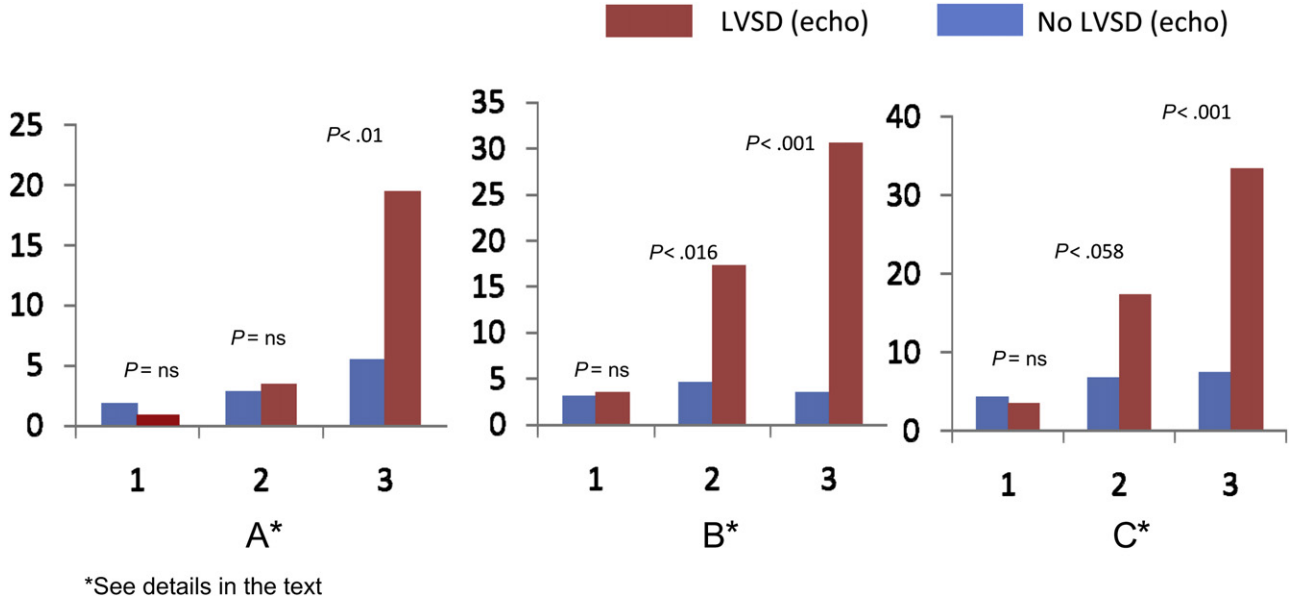

Figure 5 Incremental value of echocardiography in the three groups of cardiovascular risk factors in the presence or absence of left ventricular systolic dysfunction (echocardiography). *LVSD*, Left ventricular systolic dysfunction.

Italian Regions. The following echolabs agreed to take part in the study: Bergamo-Gavezzeni Hospital (Sganzeria P, Passaretti B), Biella Hospital-Cardiology (Marcolongo M, Tomasini B), Bologna-Bellaria Hospital-Cardiology (Pinelli G, Labanti G), Bolzano Hospital-Cardiology (Pitscheider W, Erlicher A), Catania-Ascoli Tomasello Hospital-Cardiology (Vanaria D, Carnemolla G), Catania-University Hospital-Cardiology (Sorrentino F, Monte I), Como-Valduce Hospital (Santarone M, Corrado G), Faenza Hospital-Cardiology (Casanova R, Jacopi F), Frascati Hospital-Cardiology (Giorgi G, Verallo P), Frosinone Hospital-Cardiology (Faticanti G, Paniccia V), Gubbio Hospital-Cardiology (Mandorla S, De Santis MT), Messina-University Hospital-Cardiology (Arrigo F, Zito C), Milano-National Institute Tumor (Puotti P, Materazzo C), Moncalieri Hospital (Lavezzaro GC, Parrini I), Napoli-Monaldi Hospital-Cardiology (Mininni N, Caso P), Salerno-S. Giovanni Di Dio Hospital-Cardiology (Di Leo L, De Cristofaro M), Sorrento Hospital-Cardiology (Astarita C, Liguori E), Trieste-Maggiore Hospital-Cardiovascular Center (Scardi S, Pandullo C), Udine-S. Maria della Misericordia Hospital-Cardiology (Badano L).

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