View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Directory of Open Access Journals

Awareness and appropriateness of the management of preclinical heart failure in outpatient clinics In Italy: Insights from the VASTISSIMO study

EValuation of the AppropriateneSs of The preclInical phase (Stage A and Stage B) of Heart Failure Management in Outpatient Clinics in Italy

Gian Francesco Mureddu[1,2], Stefano Nistri[3,4], Anna Maria Gori[5], Pompilio Faggiano[1,6], Biagio Fimiani[3,7], Antonio Maggi[3,8], Gianfranco Misuraca[1,9], Massimo Uguccioni[1,10], Luigi Tavazzi[11], Giovanni Battista Zito[3,12] on the behalf of the VASTISSIMO Study Group*

[1]Associazione Nazionale Medici Cardiologi Ospedalieri, Florence; [2]Cardiac Rehabilitation Unit, San Giovanni-Addolorata Hospital, Rome; [3]Associazioni Regionali Cardiologi Ambulatoriali (ARCA), Rome; [4]Cardiology Service, CMSR Veneto Medica, Altavilla Vicentina (VI); [5]Experimental and Clinical Medicine, University of Florence; [6]Cardiology Unit, Spedali Civili, Brescia; [7]Cardiology Service, ASL 3, Salerno; [8]Cardiology Unit, Fondazione Poliambulanza, Brescia; [9]Cardiology Department, Hospital SS. Annunziata, Cosenza; [10]Division of Cardiology, S. Camilllo Forlanini Hospital, Rome; [11]Maria Cecilia Hospital GVM Care & Research, Cotignola (RA); [12]Cardiology Service, ASL Napoli 3 Sud, Pompei (NA), Italy

**VASTISSIMO Study Group in Appendix*

Non-commercial use only

Abstract

A key factor in cardiovascular prevention is the detection and appropriate management of preclinical heart failure (HF), but information on the subject is scarce. We designed VASTISSIMO as a prospective, observational study to investigate Outpatient Clinic Cardiologists' skills in detecting and managing preclinical HF in Italy. Quality scores were used to assess the appropriateness of clinical management according to guideline recommendations. The feasibility of making a diagnosis of preclinical HF in a cardiology outpatient clinical setting, cardiologists' awareness of preclinical HF and consistency between physician's perceived risk of HF and the patient's classification into the preclinical HF Stages A [(SAHF) or B (SBHF)] have been investigated. Consistency was defined acceptable if the concordance between perceived risk and actual risk was >70%. Out of 3322 patients included in the study data necessary for identifying SBHF were collected in 2106 (63.4%). Many SBHF patients had their risk underestimated: 16.2% of those with previous acute myocardial infarction (AMI), 23.1% with left ventricular hypertrophy (LVH) at ECG/echocardiography, 30% with systolic/diastolic dysfunction, and 14.3% with valve disease. Cardiologists' awareness of preclinical HF in the outpatient setting should be improved. This is a critical area of cardiovascular prevention that requires attention to improve good clinical practice and adherence to guidelines.

Correspondence: Gian Francesco Mureddu, Division of Cardiology and Cardiac Rehabilitation Unit, San Giovanni-Addolorata Hospital, Via dell'Amba Aradam 9, 00184 Roma, Italy.
Tel. +39.06.77055637 - Fax: +39.06.77056715.
E-mail: gfmureddu@tiscali.it

Conflict of interest: The authors have no conflict of interest to disclose.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Key words: Preclinical heart failure; preventive cardiology; HF stages management; clinical awareness.

Received for publication: 1 November 2018.
Accepted for publication: 3 January 2019.

©Copyright G.F. Mureddu et al., 2019
Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2019; 89:1006
doi: 10.4081/monaldi.2019.1006

This article is distributed under the terms of the Creative Commons Attribution Noncommercial License (by-nc 4.0) which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

Introduction

Heart failure (HF) is a pandemic with a progressively increasing prevalence mainly due to population growth and aging [1,2]. The first action needed to counteract this major public health problem is to tackle it at its early stages [3]. Since 2005 [4-7] and until now [8,9] both American (ACC/AHA) and European (ESC) scientific guidelines recognize four stages of HF that identify the progression of the disease from the simple exposure to risk factors up to the onset of symptoms. In particular, subjects at risk of developing HF are in stage A HF (SAHF) whereas asymptomatic patients with left ventricular (LV) damage (structural and/or functional abnormalities increasing the likelihood of developing overt HF), are in Stage B HF (SBHF) [4-9]. Such classifications have demonstrated to give important prognostic information [10]. Thus, given the progressive nature of HF, characterized by a long-lasting preclinical phase [11], early interventions to prevent the disease are hypothetically possible and efficacious [3,12].

pagepress

However, previous observations have shown that physicians' awareness even about clinical HF is lower than it should be, with HF being perceived as less important than other chronic diseases such as cancer which is the major concern among the general public [13]. Moreover, the awareness of HF management among different categories of physicians (cardiologists, internists, geriatricians and primary care physicians) has been reported to be suboptimal in European countries including Italy, and in each discipline, there is insufficient adherence to guideline-recommended management strategies [13,14]. To date the awareness of cardiologists in detecting and managing the *preclinical* stages of HF has not been investigated and it is unclear how far the Italian cardiologists are familiar with such recommendations. This is an important issue since the frequency of preclinical HF has been reported to exceed 50% in community-dwellers [15-18]. Hence, the capability of detecting SAHF and SBHF is a pivotal step for implementing effective strategies to prevent HF, including lifestyle changes and appropriate pharmacologic therapies [10-12,19].

VASTISSIMO (EValuation of the AppropriateneSs of The preclInical phase [Stage A and Stage B] of heart failure Management in Outpatient clinics in Italy) is a prospective, observational study designed to investigate the appropriateness of medical practice among cardiologists as regards the early detection and management of preclinical HF (stratified as SAHF and SBHF) [20].

Methods

VASTISSIMO consisted in a data collection carried out during the routine clinical visits scheduled at the outpatient clinics of general cardiology as a part of an educational project. Details of the study were previously reported [20]. Briefly, a total of 80 cardiologists working in Outpatient clinics were selected, excluding those working in HF-dedicated facilities. The cardiologists invited to participate in the study had been informed about the study as being an 'observational study followed by a web-based educational program'. Participating physicians were uniformly distributed throughout Italy and were required to have an average routine practice of ≥60 patients per week. The flow chart of the study is reported in Box 1.

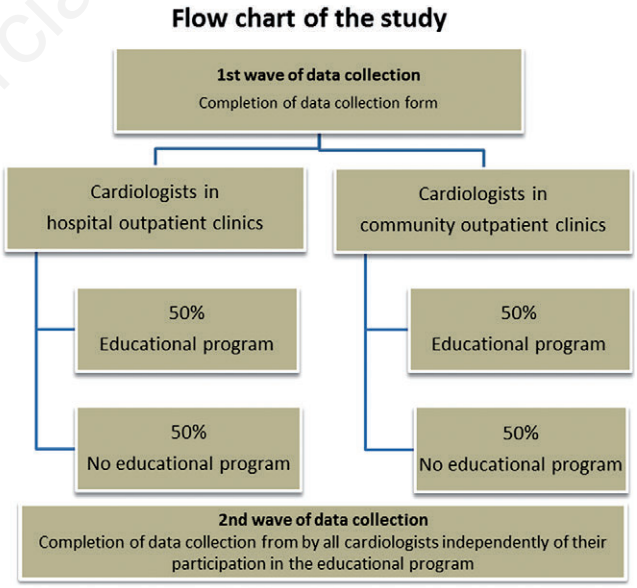
Over a predefined period of one month from June 24th 2013 to October 22nd 2013, the participating physicians selected consecutive patients, aged 35 years or older, without previous or prevalent HF after obtaining informed consent for the treatment of their personal data. Exclusion criteria included severe liver and/or renal failure requiring dialysis and/or life expectancy <1 year. Patients' data were collected and entered into a web-based case report form (CRF) [20]. The CRF included a final question regarding the clinical judgement of the cardiologist on the patient's risk of HF: *"Is the patient at risk of heart failure?"*. This final clinical opinion was subsequently matched with collected data, to assess the consistency of the clinical judgment with the patient's actual HF stage. For the purposes of this study, two different HF definitions were used: i) the original classification proposed by the 2005 AHA/ACC guidelines, and ii) a more extensive one including markers of Stage B of HF such as peripheral vascular disease, atrial fibrillation, stroke or TIA, electrocardiogram (ECG)- and/or echocardiography-detected structural or functional LV abnormalities, and chronic kidney disease [19-27] (Table 1).

The appropriateness of the management of Stages A and B of HF was investigated in terms of: i) feasibility of making a diagnosis (*i.e.*, number and percentage of fields filled in each CRF box); and ii) awareness of the cardiologist about patient's risk of HF. This last point was assessed as the consistency between the physician's perceived risk of HF for that patient and the actual classification into Stages A or B of HF based on the available data. Consistency was defined acceptable if the concordance between perceived risk and actual risk was >70%. In addition, two ad-hoc management scores were created in order to check the appropriateness of the management of patients in both SAHF and SBHF. A third score evaluated the appropriateness of pharmacological decision-making in patients identified at high risk (SBHF) (Supplementary Table S1).

Statistical analysis

Data were reported as mean±SD for continuous variables normally distributed and as median and interquartile range (IQR) for skewed variables. Categorical variables were reported as frequencies and percentages. Between-group comparisons were performed using the Chi-square test. A value of $p<0.05$ was considered statistically significant.

Non-commercial use only



Box 1. Flow chart of the study. In phase 1, the participant cardiologists in each outpatient clinic will enroll all consecutive eligible patients in a predefined period of 1 month after the start-up investigator meeting has taken place, and will fill out for each patient a data collection form. At the end of the first phase of data collection, a distance-learning (web-based) educational program will be provided to half of the cardiologists participating in the study, randomly selected. The online course (available on the same website for 3 months) consists of learning modules on the preclinical phase of heart failure that covered information of guidelines and scientific statements. At the end of the distance-learning course, a second phase of data collection will take place, with a new selection of consecutive eligible outpatients over a period of 1 month, as per in phase 1.

OPEN ACCESS

Results

Feasibility

Overall 3322 patients were enrolled over a period of four weeks. The percentage of patients with available data was 83.5%. Baseline characteristics of study population are shown in Table 2. Systolic and diastolic BP, body weight and height were almost always recorded whereas waist circumference was measured in about half cases only (49.3%). Three-quarters of patients had a lipid assessment available at the end of the visit whereas fasting glycemia was collected or requested in more than 80% of cases. As expected, the prevalence of risk factors was high. Overall, metabolic abnormalities of were detected in a in a fairly high percentage of cases. Data from the medical history were recorded in >80% of patients (Table 2, left columns). About a quarter of patients had a previous diagnosis of coronary heart disease (CHD), and about 20% had atherosclerosis in another vascular bed. Atrial fibrillation (AF) accounted for 18% of the total study population (574/3167) considering both patients who showed AF at the ECG (8.6%,) and those with a history of paroxysmal (8.9%) or persistent AF (8.5%). Medications at entry were all well recorded (in >80% of patients) reaching 100% for statins, angiotensin II receptor blockers (ARBs), oral anticoagulants and most glucose-lowering agents (Table 2).

Table 3 shows the availability (in percentage of patients) of both ECG and Doppler echocardiography examinations (left columns). Whilst the ECG was almost always available, a Doppler echocardiogram was recorded in 1794 out of 3305 (54%) of patients. The number of available echocardiograms rose to 67% in the 844 patients with a history of MI. However, in 43% of cases only the LV ejection fraction (LVEF) was reported in the CRF. Table 3 also shows the percentages of the abnormalities detected by ECG and Doppler echocardiography (upper panel). Prevalence of ECG-detected left ventricular hypertrophy (LVH) was about 18%, mostly due to signs of LV strain (17%). As expected, the prevalence of echocardiographically-detected LVH was higher (43%) than that the ECG detected LVH, and rose to 74% when the increase of septal thickness alone was considered as a surrogate index of increased LV mass. Among other organ damage (OD) markers, both left atrial dilation and LV diastolic dysfunction were highly prevalent.

Consistency

Almost all cardiologists (99.7%) evaluated patients' HF risk exposure by answering the end-of-page question "*Is the patient at risk of heart failure?*" They estimated 1115 patients (34.3%) as not at risk *versus* 2140 patients (65.4%) at risk of incident HF (Figure 1, left upper panel). The concordance between the cardiologists' perceived risk of HF and the real prevalence of SBHF is shown in Figure 1. Patients with data available to identify stage SBHF were 2106 out of 3322 (63.4%). Among those with data, we were able to re-classify 1749 cases as actually in SBHF (83.0%) and 357 (17.0%) SAHF accordingly with the ACC/AHA classification. Thus, a relevant proportion of patients with SBHF had been misclassified whether using the ACC/AHA classification (Figure 1, right upper panel) or the more extensive "per-protocol" definition of SBHF (Figure 1, left lower and right lower panels).

Appropriateness of SAHF and SBHF management

Figure 2 shows the results concerning the appropriateness of the management of SAHF patients based on the AHA/ACC classification. Considering all the actions that the Cardiologist had performed to stratify patients as SAHF, the appropriateness score was

Non-commercial use only

Table 1. Definition of stages of HF used in the current study.

Stage A (AHA/ACC)	Stage B (ACC/AHA)	Stage B (extensive definition)
Arterial hypertension	Previous acute myocardial infarction (MI)	Previous acute myocardial infarction (MI) or chronic ischemic heart disease (stable angina or history of revascularization (CABG/ PCI)
Diabetes mellitus	LV hypertrophy at ECG or echocardiography	Stroke or transient ischemic attack (TIA)
Obesity (BMI >30 Kg/m^2)	LV systolic dysfunction (EF <50%)	Peripheral vascular disease, carotid disease, or abdominal aortic aneurysm either clinical or subclinical
Metabolic syndrome (ATP III criteria)	Diastolic dysfunction	Chronic atrial fibrillation (permanent)
Familiar history of idiopathic cardiomyopathy	Any valvular heart disease at least or more than moderate	LV hypertrophy at ECG (voltage-duration or Perugia strain criteria)
Subjects using cardiotoxins		Left bundle branch block (LBBB) Structural LV abnormalities detected at echocardiography • LV hypertrophy (LV mass >95 g/m^2 in females or >115 g/m^2 in males) • Concentric remodeling (RWTd >0.42) • LV dilation (LV EDV >95 ml/m^2) • LA dilation (LA volume >34 mL/m^2) • LV systolic dysfunction EF <50% Diastolic dysfunction (multiparametric, see ref 17,19) • E/e' >15 or • r E/e'>8 + LVH or LA dilation Any valvular heart disease at least or more than moderate Kidney chronic disease, KDOQI class ≥3[1] • GFR <60ml/min*1.73/m^2 or microalbuminuria

Subjects with arterial hypertension, type-2 diabetes mellitus, obesity (BMI >30 Kg/m^2), metabolic syndrome (ATP III criteria), individuals exposed to cardiotoxic antiblastic drugs (administration >250 mg/m^2, adriamycin, >300 mg/m^2 epirubicin), or family history of idiopathic cardiomyopathy are classified as in stage A of HF accordingly with guidelines [4-6,8]. Stage B of HF comprises subjects with as previous acute myocardial infarction (MI), LV hypertrophy at ECG or echocardiography, LV systolic dysfunction (EF <50%) or diastolic dysfunction in the absence of symptoms, any valvular heart disease at least or more than moderate accordingly with the ACC/AHA 2009 guidelines definition [8]. [1]men >class 3a (GFR<60 ml/min), women >class 3b (GFR<45 ml/min).

Table 2. Baseline characteristics of the study population.

Demographic and anthropometric data	N with data (%)	Mean±SD
Age (yrs) *(mean±SD)*	3322 (100)	67.1±11.9
Male *(n, %)*	3322 (100)	1810 (54.5)
Weight (kg) *(mean±SD)*	2980 (89.7)	77.1±14.9
Height (cm) *(mean±SD)*	3002 (90.4)	166.0±8.8
BMI (kg/m^2) *(mean±SD)*	2977 (89.6)	28.0±4.9
Systolic blood pressure (mmHg) *(mean±SD)*	3280 (98.7)	134.6±17.7
Diastolic blood pressure (mmHg) *(mean±SD)*	3283 (98.8)	79.4±9.8
Heart rate (bpm) *(mean±SD)*	3268 (98.4)	71.3±12.5
Risk factors	**N with data (%)**	**Prevalence N (%)**
Smoking habit *(n, %)* *current former (>1yr)*	3178 (95.7) 2949 (88.8)	605 (19.0) 870 (29.5)
Arterial hypertension *(n, %)*	3279 (98.7)	2830 (85.2)
Hypercholesterolemia *(n, %)*	3036 (91.4)	1897 (62.5)
Hypertriglyceridemia *(n, %)*	2865 (86.2)	770 (26.9)
Type 2 diabetes mellitus *(n, %)*	3092 (93.1)	956 (28.8)
Obesity (BMI³ 30 kg/m^2) *(n, %)*	3179 (95.6)	1033 (32.5)
Metabolic syndrome *(n, %)*	2842 (85.6)	683 (24.0)
Fasting hyperglycemia *(n, %)*	2688 (80.9)	662 (24.6)
Impaired glucose tolerance (IGT) *(n, %)*	2213 (66.6)	342 (15.5)
Obstructive sleep apnea syndrome (OSAS)	2695 (81.1)	158 (5.8)
Medical history	**N with data (%)**	**Prevalence N (%)**
CHD/revascularization *(n, %)*	3203 (96.4)	798 (24.9)
Myocardial infarction *(n, %)*	3197 (96.2)	576 (18.0)
Stroke/TIA *(n, %)*	3184 (95.8)	265 (8.3)
Peripheral artery disease *(n, %)*	2798 (84.2)	361 (12.9)
Paroxysmal atrial fibrillation *(n, %)*	3141 (94.6)	296 (8.9)
Persistent atrial fibrillation *(n, %)*	3170 (95.4)	271 (8.5)
Valvular disease *(n, %)*	2999 (90.3)	347 (10.4)
Carotid atherosclerosis *(n, %)*	2482 (74.7)	762 (30.7)
COPD *(n, %)*	3140 (94.5)	479 (14.4)
Use of cardiotoxic drugs, (previous or current)	3167 (95.3)	128 (4.0)
Medications at entry	**N with data (%)**	**Drugs in pts with data N (%)**
Antiplatelet drugs *(n, %)*	3156 (95.0)	1627 (51.6)
Statins *(n, %)*	3322 (100)	1622 (48.8)
Beta blockers *(n, %)*	3112 (93.7)	1325 (42.6)
Ivabradine *(n, %)*	3284 (98.9)	40 (1.2)
ACE-inhibitors *(n, %)*	3126 (94.1)	1430 (45.7)
ARBs *(n, %)*	3322 (100)	916 (27.6)
Aldosterone receptor blockers *(n, %)*	3230 (97.2)	147 (4.6)
Loop diuretics *(n, %)*	3322 (100)	458 (13.8)
Calcium antagonists *(n, %)*	3193 (96.1)	790 (24.7)
Oral anticoagulants *(n, %)*	3322 (100)	299 (9.0)
NOACS *(n, %)*	3298 (99.3)	6 (0.2)
Ranolazine *(n, %)*	3280 (98.7)	34 (1.0)
Nitrates *(n, %)*	3322 (100)	208 (6.3)
Thiazide diuretics *(n, %)*	3191 (96.1)	733 (23.0)
Insulin *(n, %)*	3306 (99.5)	210 (6.4)
Metformin/other *(n, %)*	3322 (100)	791 (23.8)
Bronchodilators *(n, %)*	3305 (99.5)	181 (5.5)

Non-commercial use only

good or very good in most cases (86.2% of total observations) and insufficient in only 13.8% of cases (Figure 2, lower right). The appropriateness of the management of SBHF patients is shown in Figure 3. The appropriateness score was insufficient in the majority of cases (63%) while only in 13.2% of cases did Cardiologists attain a score of "very good" and in 23.7% a score of "good " (Figure 3, right panel). Table 2 (mid and lower panels) shows the diagnostic tests and laboratory examinations the Cardiologists requested at the end of the visit. Doppler echocardiography was the most requested test followed by ultrasound scan of the carotid, ultrasound scan of the peripheral arteries and ultrasound scan of the abdominal aorta. Among laboratory examinations, most of them were requested in more than 30% of cases. BNP (9.3%) and/or NT-pro BNP (15.45) in less than 25% of cases.

The therapeutic decision-making appropriateness in patients in Stage B of heart failure was generally satisfying. In patients with previous AMI, at least three of four evidence-based (EB) drugs (beta-blockers, angiotensin-converting enzyme inhibitor (ACE-i/ARBs, statins, antiplatelet agents) were already being taken or were prescribed at the end of the visit, accounting for 89.5% of patients. In patients at high risk with organ damage as in the case where LVH was detected, a renin-angiotensin inhibitor or an aldosterone antagonist was already being taken or prescribed in 83.5% of the study population (Supplementary Table S1).

Discussion

The main findings of our study are that among the Cardiologists involved in the study: 1) the management of subjects at risk (SAHF) is generally good; 2) the high number of unavailable or non-recorded data affects the feasibility of correctly recognizing SBHF; and 3) the management of SBHF appears to be adequate in just slightly more than one-third of cases.

The current guidelines reaffirm the concept that the onset of HF may be delayed (or prevented) through interventions "aimed at modifying risk factors for HF or treating asymptomatic LV systolic dys-

Non-commercial use only

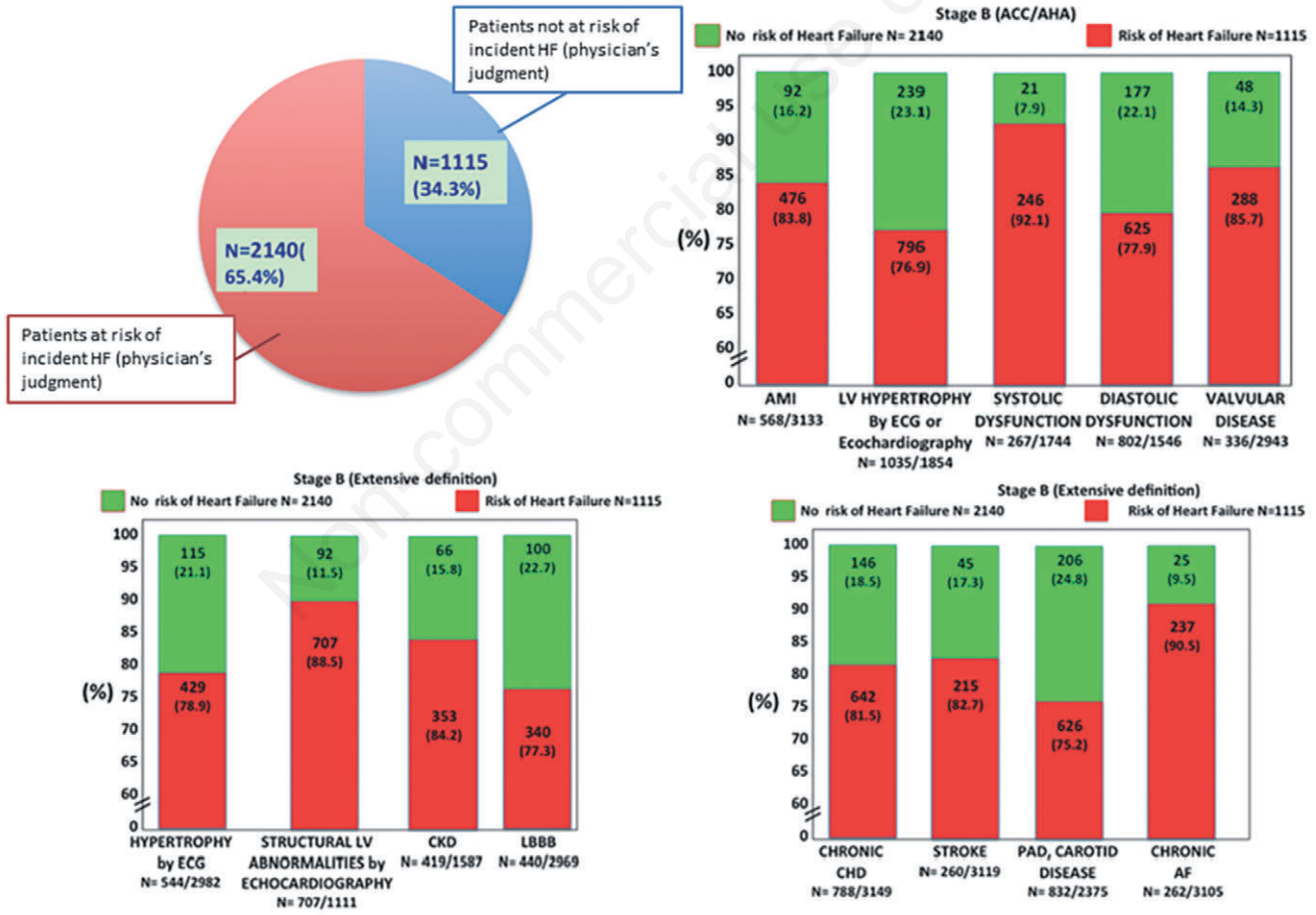


Figure 1. Consistency between Clinicians' perceived risk of HF and actual patients' classification into stage B of HF. Left upper panel: the pie shows the percentage of patients classified "at risk of heart failure" by Cardiologist on their clinical judgment (perceived risk of HF); 1115 patients (34.3%) were estimated as not at risk of incident HF (blue) whereas 2140 patients (65.4%) were considered at risk of incident HF (red). Right upper panel: the bars show the concordance between the cardiologists' perceived risk of HF and the real prevalence of SBHF matched with the ACC/AHA classification of heart failure stages; a relevant proportion of patients with ascertained SBHF (red bars) were misclassified (green bars). Lower left and right panels: the bars show the concordance between the cardiologists' perceived risk of HF and the real prevalence of SBHF as compared with the extensive definition of SBHF; patients with ascertained SBHF (per-protocol definition) are shown in red bars whereas those misclassified are shown with the green bars.

function" [8,9]. The prevalence of subjects at risk of HF is high. In the Atherosclerosis Risk in Communities study (ARIC) in 15 792 middle-age subjects enrolled between 1987 and 1989, only 5% of participants were free of HF risk factors or structural heart disease (Stage 0), whereas 52% were categorized as SAHF, 30% SBHF, 7% Stage C1 (symptomatic HF), and 6% Stage C2 (hospitalized for HF). Left ventricular ejection fraction was preserved in 77% SAHF and SBHF and 65% Stages C patients, respectively [28].

Whilst in contemporary symptomatic chronic HF patients a benefit from the adherence to recommended pharmacological therapy is unquestioned [29], and most of the non-adherence was explained by comorbidities or intolerance [8,9,14,15], management of preclinical

Table 3. Electrocardiogram, echocardiographic of the study population available at entry and other diagnostic tests requested at the end of the medical examination and laboratory tests available at entry examination or requested at the end of the examination.

Diagnostic tests	N with data (%)	Prevalence in pts with data N (%)
Electrocardiogram *(EKG) (n, %)*	3305 (99.5)	
Sinus rhythm *(n, %)*	3142 (94.6)	2813 (89.5)
Atrial fibrillation *(n, %)*	3142 (94.6)	271 (8.6)
Unspecified *(n, %)*	3142 (94.6)	180 (5.4)
Pacemaker *(n, %)*	3142 (94.6)	58 (1.8)
Bundle branch block *(n, %)*	3015 (90.8)	456 (15.1)
Left ventricular hypertrophy *(n, %)*	3029 (91.2)	557 (18.4)
Left ventricular strain *(n, %)*	3003 (90.4)	516 (17.2)
Abnormal Q waves *(n, %)*	3005 (90.5)	335 (11.1)
Doppler echocardiography	1794 (54.0)	
Left Ventricular (LV) hypertrophy *(n, %)*	1729 (52.0)	744 (43.0)
Interventricular septal thickness >12 mm *(n, %)*	1699 (51.1)	1255 (73.9)
LV Systolic dysfunction *(n, %)*	1774 (53.4)	273 (15.4)
LV dilation *(n, %)*	1697 (51.1)	179 (10.5)
Left atrial dilation *(n, %)*	1695 (51.0)	746 (44.0)
Diastolic dysfunction *(n, %)*	1576 (47.4)	821 (52.1)
Diagnostic tests	**Requested at the end of the examination N (%)**	
Doppler echocardiography *(n, %))*	1442 (43.4)	
Carotid ultrasound *(n, %)*	1250 (37.6)	
Aortic echography *(n, %)*	175 (5.3)	
Peripheral vascular Doppler *(n, %)*	241 (7.3)	
Cardiac MRI *(n, %)*	14 (0.4)	
Exercise ECG *(n, %)*	496 (14.9)	
Stress echo *(n, %)*	124 (3.7)	
Myocardial scintigraphy *(n, %)*	97 (2.9)	
Coronary CT *(n, %)*	11 (0.3)	
Coronary angiography *(n, %)*	51 (1.5)	
Nocturnal saturation *(n, %)*	55 (1.7)	
Polysomnography *(n, %)*	54 (1.6)	
Laboratory test	**Available at the examination N (%)**	**Requested at the end of the examination N (%)**
BNP *(n, %)*	36 (1.1)	310 (9.3)
NT-pro BNP *(n, %)*	44 (1.3)	512 (15.4)
Hemoglobin *(n, %)*	1558 (46.9)	1075 (32.4)
Glycemia *(n, %)*	1685 (50.7)	1105 (33.3)
Serum Creatinine *(n, %)*	1616 (48.6)	1199 (36.1)
Potassium *(n, %)*	1372 (41.3)	1201 (36.2)
Total cholesterol *(n, %)*	1641 (49.4)	1153 (34.7)
HDL cholesterol *(n, %)*	1475 (44.4)	1167 (35.1)
Triglycerides *(n, %)*	1526 (45.9)	1164 (35.0)
Glycated hemoglobin *(n, %)*	430 (12.9)	894 (26.9)
Albuminemia *(n, %)*	268 (8.1)	537 (16.2)
Microalbuminuria *(n, %)*	135 (4.1)	1211 (36.5)

Non-commercial use only

HF is more difficult and drug therapy still debated. The Study of Heart Failure Awareness and Perception in Europe (SHAPE) [13], a survey specifically designed to test the awareness and perception of clinical HF among European clinicians (cardiologists, internists, geriatricians, and primary care physicians), demonstrated a poor adherence to guideline-recommended management strategies.

Actually, identifying the preclinical stage of HF may be more difficult than identifying clinical HF [21-30]. This is particularly true for HF with preserved ejection fraction (HFpEF), a condition highly prevalent [15,18] in the elderly [18,26], with a progressively rising incidence [31,32] and requiring a complete echocardiographic evaluation and a multiparametric approach [15,16,18-21] for a reliable diagnosis.

In the Italian Health care system, outpatient cardiologists should evaluate patients at CVD risk sharing them with the General Practitioners (GPs). Thus, outpatient cardiologists should often have the chance of detecting subjects at high risk of HF (SAHF and SBHF) and, therefore, the opportunity of implementing effective strategies to prevent HF, including lifestyle changes and appropriate pharmacologic therapies. How this clinical path is actually carried out in clinical practice generates the questions that the VASTISSIMO study sought to address: are Cardiologists sufficiently alert to identify those patients at risk of developing HF in clinical practice? Are they operating "appropriately" in this regard? Our findings showed that it was not possible to detect or exclude preclinical HF (even considering only the ACC/AHA criteria) in 1216 of the 3322 patients (36.6%) due to the incompleteness of the collected patient data.

It has been shown that the availability of data or simply just having a patient database is associated with a gain in quality and appropriateness of care [33]. Actually, in the present study, the Cardiologists' awareness of the HF risk, investigated in terms of the consistency between the Cardiologist's perceived risk of HF in a patient and the patient's actual classification as SAHF or SBHF, was lower than expected, and even the presence of objective markers of organ damage did not lead to correctly classifying those patients as at high risk. This seems to be independent both of the type of classification and of the type of available diagnostic tests. The clinical setting also did not affect the behavior of the Cardiologists, since no significant difference was detected in the patient management between physicians working in primary-care Outpatient clinics or those working in hospital-related Outpatient clinics.

Non-commercial use only

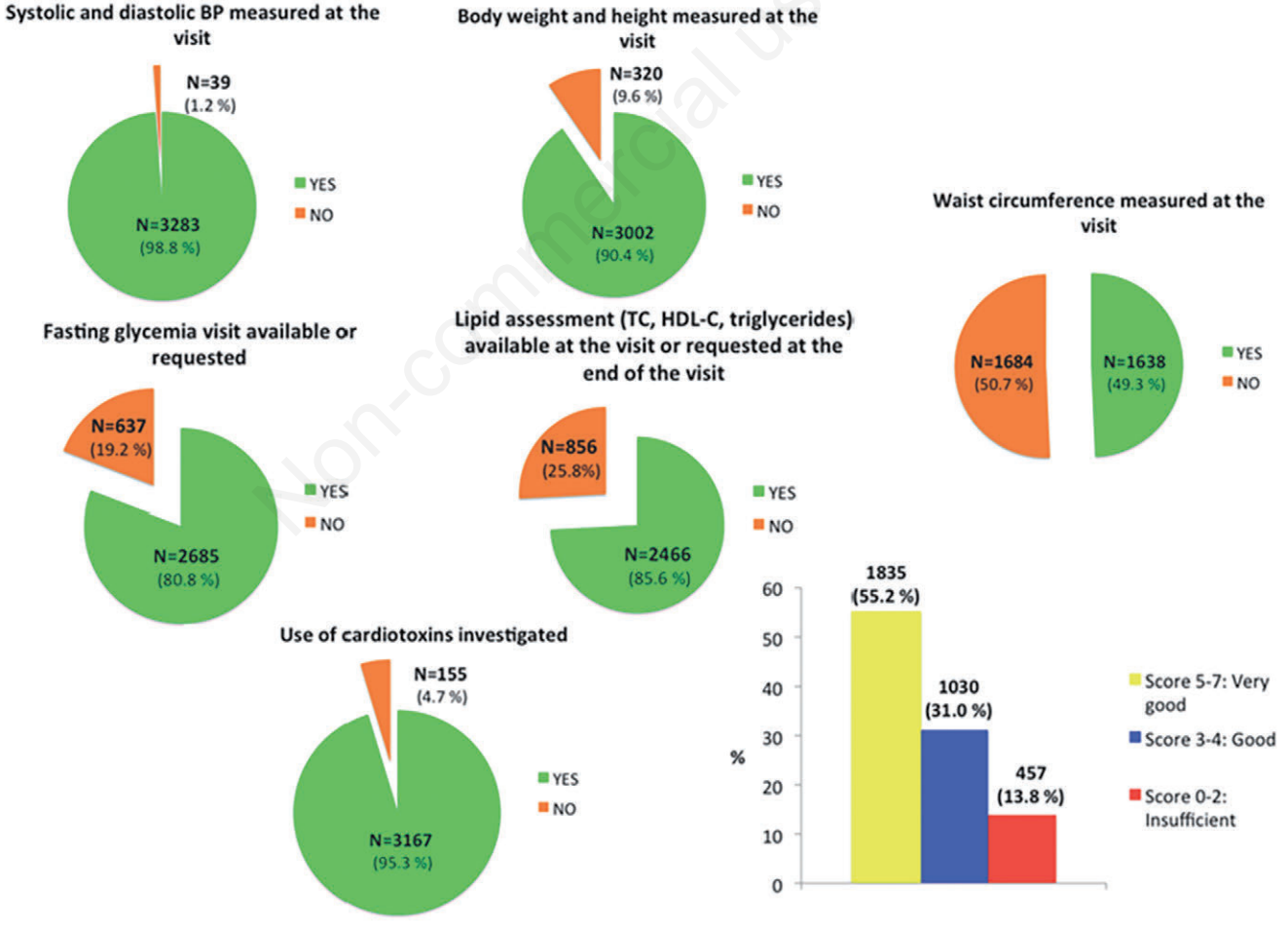


Figure 2. Stage A Heart failure appropriateness of management score. The results evaluating the appropriateness of the management of patients in SAHF based on the AHA/ACC classification are shown. The pies show the percentage of available (green) or not available (orange) records constituting the SAHF appropriateness score (see text for further explanation). Right lower panel: bars showing the appropriateness score for stratifying patients in SAHF (see text for further explanation).

Surprise may also arise from the observation of how cardiologists manage patients at different level of risk. While the appropriateness of management score for Stage A patients was on average high (*i.e.*, all the data required for risk stratification were available or required at the end of the visit) this was not so for patients in Stage B in whom the appropriateness of management score was suboptimal. The quantification of both ventricular systolic and diastolic function, and the measurement of LV mass or left atrial volume do not seem to be considered as much valuable, maybe recognizing SBHF does not perceived as prognostically relevant or obtaining a complete LV diastolic function assessment/quantifying LV mass may be considered time consuming [34]. Furthermore, many of the SBHF-related preclinical abnormalities can be detected only during exercise, making the evaluation of Stage B particularly complex in the outpatient setting [35]. Similarly, clinical cardiologists underuse BNP [36], and even valve disease remains undiagnosed [37,38].

Finally, it seems that symptoms rather than the epidemiological and pathophysiological framework are the main factors guiding the clinical management in SBHF. This it is partly justified by the fact that the level/quality of evidence regarding medical therapy is poor or questionable in SBHF and scarce in particular for HFpEF [9]. What emerges from this survey is a general "regression" to basic clinical practice with a consequent loss of diagnostic sensitivity. The pharmacological decision-making process seems to be generally appropriate since the evidence-based drugs were prescribed in over 80% of patients at high risk. However, the study design did not allow us to evaluate the appropriateness in terms of targets achieved and/or medication dosage. This study confirms our previous observation in an epidemiological setting: in the Predictor study [18], 48% of patients in stage B of HF had risk factors not at target level; even in Stage C (overt HF) 15% of patients were not on an ACE-i or beta-blocker or aldosterone antagonist.

Study limitations

Our study has several limitations. First, cardiologists' participation was voluntary and consecutiveness of enrollment was not verified, thereby a selection bias cannot be ruled out, and a special care of physicians on the enrollees cannot be excluded. This may be considered an intrinsic feature of such a pragmatic study, that however could only worsen the recorded physicians' performance. Second, the cardiologists' diagnostic and therapeutic management was investigated through appropriateness of management scores that had been specifically created for the study, and therefore not validated in external studies. Third, the high number of not available data affects the feasibility of correctly recognizing Stage B HF. Therefore, it is plausible that there is inappropriate management in Stage B HF due to its under-recognition. Fourth, the appropriateness of drug therapy was investigated only for drug classes and not for their dosages (however, this was not a primary endpoint of the study). Finally, this study did not investigate possible causes of apparent under-treatment, such as comorbidities, intolerance or contraindications.

Conclusions

This prospective, pragmatic study provides useful contemporary information regarding the ability to recognize and caring for preclinical HF in a specific setting of outpatient cardiac clinics. This experience highlights the need of systematic educational campaigns to sensitize physicians, including cardiologists, on the awareness of preclinical HF in the clinical practice as well as of coordinated actions involving clinicians, institutions and community services.

Non-commercial use only

Condition at risk	Yes, n (%)	No, n (%)
If previous MI in the clinical history (n=576)		
Was a Doppler echocardiography available at the clinic visit or has it been requested at the end of the visit?	497 (86.3%)	79 (13.7%)
If LVH has been detected at echocardiography: (n=744)		
Has LV hypertrophy been quantified? (Box echocardiography g/m^2)	317 (42.6%)	427 (57.4%)
Has systolic dysfunction been evaluated? (EF %)	586 (78.8%)	158 (21.2%)
Has left atrial dilation been evaluated ? ml/m^2	283 (38.0%)	461 (62.0%)
Has the E/e' ratio been measured?	201 (27.0%)	543 (73.0%)
If a significant valvulopathy has been detected (n=347)		
Was Doppler echocardiography available or requested at the end of the visit?	314 (90.5%)	33 (9.5%)

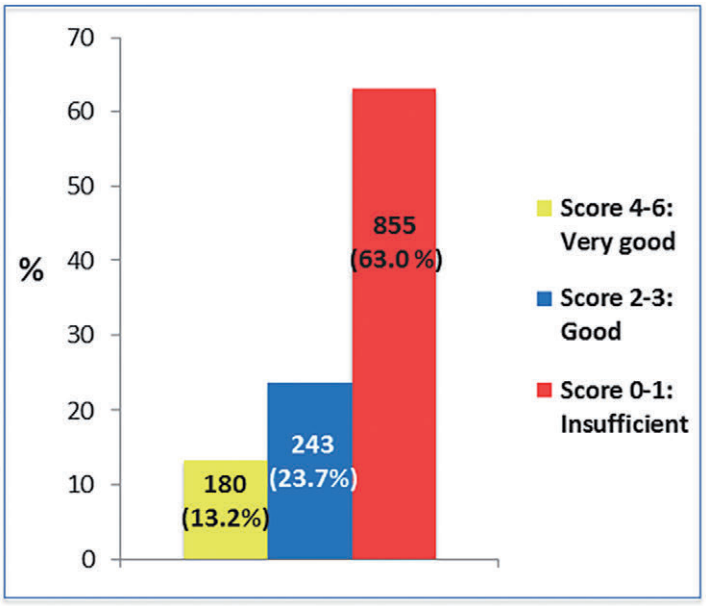


Figure 3. Stage B heart failure appropriateness of management score. Left panel: items constituting the stage B HF appropriateness diagnostic management score. Right panel: the bars show the SBHF management scores levels of appropriateness the clinicians reached along the study (percentages in brackets); red bar: insufficient appropriateness (score=0-1); blue bar. good appropriateness (score=2-3); yellow bar: very good appropriateness (score=4-6).

References

1. Roth GA, Huffman MD, Moran AE, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. N Engl J Med 2015; 372:1333-41.
2. Ma J, Ward EM, Siegel RL, Jemal A. Temporal trends in mortality in the United States, 1969-2013. JAMA 2015;314: 1731-9.
3. Braunwald E. The war against heart failure: the Lancet lecture. Lancet 2015;385:812-24.
4. Hunt SA, Abraham WT, Chin MH, et al. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2005;46:e1-e82.
5. Jessup M, Abraham WT, Casey DE, et al. 2009 Focused update: ACC/AHA 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: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119:1977-2016.
6. Swedberg K, Cleland J, Dargie H, et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Eur Heart 2005;26:1115-40.
7. Dickstein K, Cohen-Solal A, Filippatos G, et al. The Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur J Heart Fail 2008;10:933-89.
8. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776-803.
9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891-75.
10. Ammar KAl, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. Circulation 2007;115:1563-70.
11. Echouffo-Tcheugui JB, Erqou S, Butler J, et al. Assessing the risk of progression from asymptomatic left ventricular dysfunction to overt heart failure: A systematic overview and meta-analysis. JACC Heart Fail 2016;4:237-48.
12. Wang TJ, Evans JC, Benjamin EJ, et al. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003;108:977-98.
13. Remme WJ, McMurray JJV, Richard Hobbs FD, et al. Awareness and perception of heart failure among European cardiologists, internists, geriatricians, and primary care physicians. Eur Heart J 2008;29:1739-52.
14. Maggioni AP, Orso F, Calabria S, et al. The real world evidence of heart failure: findings from 41,413 patients of the ARNO database. Eur J Heart Fail 2016;18:402-10.
15. Wan SH, Vogel MW, Chen HH. Pre-clinical diastolic dysfunction. J Am Coll Cardiol 2014;63:407-16.
16. Redfield MM, Jacobsen SJ, Burnett JC, et al. Burden of systolic and diastolic ventricular dysfunction in the community. J Am Med Assoc 2003;289:194-202.
17. Davies MK, Hobbs FR, Davis RC, et al. Prevalence of left-ventricular systolic dysfunction and heart failure in the Echocardiographic Heart of England Screening study: a population based study. Lancet 2001;358:439-44.
18. Mureddu GF , Agabiti N, Rizzello V, et al. Prevalence of preclinical and clinical heart failure in the elderly. A population-based study in Central Italy. Eur J Heart Fail 2012;14:718-29.
19. Vasan RS., Benjamin EJ. The future of cardiovascular epidemiology. Circulation 2016;133:2626-33.
20. Mureddu GF, Nistri S, Faggiano P, et al. Evaluation of the appropriateness of the preclinical phase (stage A and stage B) of heart failure Management in Outpatient clinics in Italy rationale and design of the 'VASTISSIMO' study. J Cardiovasc Med (Hagerstown). 2016;17:501-9.
21. Schocken DD, Benjamin EJ, Fonarow GC, et al. Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group. Circulation 2008;117:2544-65.
22. Carerj S, La Carrubba S, Antonini-Canterin F, et al. on behalf of the Research Group of the Italian Society of Cardiovascular Echography. The incremental prognostic value of echocardiography in asymptomatic stage A heart failure. J Am Soc Echocardiogr 2010;23:1025-34.
23. Mureddu GF, Tarantini L, Agabiti N, et al. Evaluation of different strategies for identifying asymptomatic left ventricular dysfunction and preclinical (stage B) heart failure in the elderly. Results from 'PREDICTOR', a population based-study in central Italy. Eur J Heart Fail 2013;15:1102-12.
24. Agarwal SK, Chambless LE, Ballantyne CM, et al. Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. Circ Heart Fail 2012;5:422-9.
25. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2016;29:277-314.
26. Butler J, Kalogeropoulos A, Georgiopoulou V, et al. Incident heart failure prediction in the elderly: the health ABC heart failure score. Circ Heart Fail 2008;1:125-33.
27. Yang H, Negishi K, Otahal P, Marwick TH. Clinical prediction of incident heart failure risk: a systematic review and meta-analysis. Open Heart 2015;2:e000222.
28. Shah AM, Claggett B, Loehr R, et al. Heart failure stages among older adults in the community. The atherosclerosis risk in communities study. Circulation 2017;135:224-40.
29. Komajda M, Böhm M, Borer JS, et al. Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis. Eur J Heart Fail 2018;20: 1315-22.
30. Maggioni AP, Anker SD, Dahlstrõm, et al. Are hospitalized or

ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. Eur J Heart Fail 2013;15:1173-84.
31. Owan TE, Hodge DO, Herges RM, et al. trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251-9.
32. Barr DA. Geography as disparity. The shifting burden of heart disease. Circulation 2016;133:1151-4.
33. Giorda CB, Guida P, Avogaro A, et al. Association of physicians' accuracy in recording with quality of care in cardiovascular medicine. Eur J Cardiovasc Prev Rehabil 2009;16:722-8.
34. Nistri S, Ballo P, Mele D, et al. Effect of echocardiographic grading of left ventricular diastolic dysfunction by different classifications in primary care. Am J Cardiol 2015;116: 1144-52.
35. Kosmala W, Jellis CL, Marwick TH. Exercise limitation associated with asymptomatic left ventricular impairment analogy with Stage B Heart Failure. J Am Coll Cardiol 2015;65: 257-66.
36. Boffa U, McGrady M, Reid CM, et al. SCReening Evaluation of the Evolution of New Heart Failure Study (SCREEN-HF): early detection of chronic heart failure in the workplace. Aust Health Rev 2017;41:121-6.
37. d'Arcy JL, Coffey S, Loudon MA, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J 2016;37: 3515-22.
38. Marciniak A, Glover K, Sharma R. Cohort profile: prevalence of valvular heart disease in community patients with suspected heart failure in UK. BMJ Open 2017;7:e012240.

VASTISSIMO Study Group

Reviewers: Emilia Chiuini (ASL 1, Perugia), Francesco Fattirolli (Department of Experimental and Clinical Medicine, AOU Careggi, Florence), Raffaele Griffo (Cardiac Rehabilitation Unit, Department of Cardiology, La Colletta Hospital, Arenzano, GE), Franco Guarnaccia (Angiocard Center, Naples), Maria Gabriella Pinzagli (ASL 1, Perugia), Pier Luigi Temporelli (Division of Cardiac Rehabilitation, Fondazione Salvatore Maugeri, IRCCS, Veruno, NO), Italy.

Participating centers and clinical investigators affiliations: M.G. Abrignani (ANMCO, Trapani); L. Adesso (ARCA, Salerno); K. Al Yassini (ARCA, Ferrara), M. Ambrosetti (ANMCO, Varese); E. Antoncecchi (ARCA, Bari); F. Antonini-Canterin (ANMCO, Pordenone); S. Aprile (ARCA, Naples), M.A. Barberis (ARCA, Florence); G. Bisignani (ANMCO, Castrovillari); P.L. Bonati (ARCA, Parma); P. Brocco (ARCA, Roma); L. Caprini (ARCA, Brescia); G. Carella (ARCA, Napoli); A. Cherubini (ANMCO, Trieste); M. Chiatto (ANMCO, Cosenza); E. Chiuini (ARCA, Perugia); G. Cigna (ARCA, Rome); G. Cioffi (ANMCO, Trento); F. Cocco (ANMCO, Manduria); E. Coletti Moia (ARCA, Turin); N. Cosentino (ANMCO, Cariati); E. Cuozzo (ARCA, Oristano); A.G. Dato (ARCA, Paternò); S. De Feo (ANMCO, Peschiera Del Garda); S. De Spirito (ANMCO, Viterbo); C. Del Mirto (ARCA, Campobasso); D. Demarie (ANMCO, Torino); G. Fiori (ARCA, Quartu Sant'Elena); S. Frattini (ANMCO, Cremona); A. Frisinghelli (ANMCO, Garbagnate Milanese); M. Pia Fugazzaro (ARCA, Caldogno); M. Gabriele (ANMCO, Mazara del Vallo); G. Gazale (ARCA, Sassari); F. Guarnaccia (ARCA, Naples); N. Lamanna (ANMCO, Bari); S. Licata (ARCA, Licata); A. Lillo (ARCA, Bari); A. Madureri (ARCA, Salò); P. Maggi (ARCA, Brescia); A. Magliaro (ARCA, Avellino); G. Malfatto (ANMCO, Milan); M. Megatelli (ANMCO, Brescia); F. Moncada (ANMCO, Lentini); P. Monea (ARCA, Reggio Calabria); M. Offidani (ARCA, Ascoli Piceno); C. Panesi (ARCA, Pisa); G. Panzera (ARCA, Messina); S. Pede (ANMCO, Brindisi); R. Pes (ANMCO, Olbia); M.G. Pinzagli (ARCA, Perugia); A. Polesello (ARCA, Trento); G. Putorti (ARCA, Reggio Calabria); C. Rampazzo (ARCA, Vicenza); L. Rey (ANMCO, Gualdo Tadino; F. Rigo (ANMCO, Mestre); P. Roccanti (ARCA, Florence); G. Roganti (ARCA, Modena); C. Russi (ARCA, San Severo); G. Scorcu (ANMCO, Cagliari); D. Severini (ANMCO, Città Di Castello); L. Stella Brienza (ARCA, Messina); G. Susco (ARCA, Savona); L. Tarantini (ANMCO, Belluno); G. Veglia (ARCA, Matera); G. Vianello (ANMCO), Chioggia); B. Zisa (ANMCO, Catania), Italy.

Non-commercial use only