

Clinical and Echocardiographic Findings of Newly Diagnosed Acute Decompensated Heart Failure in Elderly Patients

Jeonggeun Moon,¹ Seok-Min Kang,^{1,2} In Jeong Cho,¹ Jaewon Oh,¹ Jaemin Shim,¹
Sang-Hak Lee,¹ Yangsoo Jang,^{1,2} and Namsik Chung^{1,2}

¹Cardiology Division, Yonsei Cardiovascular Hospital and Cardiovascular Research Institute,

²Brain Korea 21 Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea.

Received: February 23, 2010

Revised: June 1, 2010

Accepted: June 4, 2010

Corresponding author: Dr. Seok-Min Kang,
Cardiology Division, Yonsei Cardiovascular
Hospital and Cardiovascular Research
Institute, Yonsei University College
of Medicine, 250 Seongsan-ro,
Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-8450, Fax: 82-2-2227-7732
E-mail: smkang@yuhs.ac

The authors have no financial conflicts of
interest.

Purpose: Elderly patients (pts) (EPs; ≥ 65 years old) with newly diagnosed-acute decompensated heart failure (ND-ADHF) have not yet been studied. The aim of the present study was to investigate clinical characteristics, including echocardiographic findings and prognosis, for EPs with ND-ADHF and to compare those with non-elderly pts (NEPs). **Materials and Methods:** We retrospectively investigated 256 pts (144 males, 63.0 ± 14.8 years old) who were admitted to our hospital between January 2005 and March 2009 with ND-ADHF. Clinical characteristics and echocardiographic parameters were analyzed in EPs ($n = 135$, 58 males) and NEPs ($n = 121$, 86 males). **Results:** In intergroup comparison, female gender, diabetes mellitus, previous stroke and hypertension were more common in EPs. Body mass index (22.3 ± 4.5 vs. 24.0 ± 4.4 kg/m²), estimated glomerular filtration rate (54.8 ± 24.3 vs. 69.2 ± 30.7 mL/min/m²), C-reactive protein (28.5 ± 46.9 vs. 7.6 ± 11.6 mg/dL), hemoglobin (12.3 ± 2.1 vs. 13.6 ± 2.3 g/dL) and N-terminal pro-brain natriuretic peptide level ($10,538.2 \pm 10,942.3$ vs. $6,771.0 \pm 8,964.7$ pg/mL) were significantly different ($p < 0.05$ for all). Early mitral inflow velocity to early diastolic mitral annular velocity (E/E') was significantly higher in EPs than in NEPs (21.2 ± 9.4 vs. 18.0 ± 8.9 , $p < 0.05$). During follow-up (44.7 ± 14.5 months), there were no significant differences in in-hospital mortality, re-hospitalization and cardiovascular mortality between EPs and NEPs ($p = \text{NS}$ for all). **Conclusion:** EPs with ND-ADHF have different clinical characteristics and higher LV filling pressure when compared with NEPs. However, the clinical outcomes for NEPs with ND-ADHF are not necessarily more favorable than those for EPs.

Key Words: Acute heart failure, elderly patients, echocardiography

© Copyright:

Yonsei University College of Medicine 2011

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

The population of the elderly (≥ 65 years old) is increasing worldwide. The incidence and prevalence of congestive heart failure (CHF) escalates exponentially with age. In fact, CHF affects 6-10% of people over the age of 65, and acute decompensated heart failure (ADHF) is the most common cause for hospitalization of elderly

patients (EPs).^{1,2} ADHF may result from new onset of ventricular dysfunction or, more typically, exacerbation of chronic heart failure symptoms.³ The socioeconomic burden of CHF in the elderly is already tremendous and is expected to increase as more adults survive to old age thanks to reduced mortality from coronary heart disease and stroke.⁴

The epidemiology and optimal management of ADHF in the elderly are thought to be different in many aspects from those of relatively younger patients.¹ However, EPs are typically underrepresented in heart failure (HF) trials.⁵ Application of data from middle-aged patients with ADHF to treatment and management of EPs cannot be justified. Moreover, EPs who were investigated in previous CHF studies showed very diverse disease courses and heterogeneous chronicity.⁶⁻⁹ Accordingly, the clinical characteristics of with newly diagnosed-ADHF (ND-ADHF) in the elderly remain to be determined.

The aims of the present study were to clarify the initial clinical presentation, echocardiographic parameters and prognosis of EPs with ND-ADHF, and to compare with those of non-EPs (NEPs, < 65 years old).

MATERIALS AND METHODS

Patient characteristics

This is a single center, retrospective and observational study. Study approval was obtained from the Institutional Review Board of Yonsei University College of Medicine. Between January 2005 and March 2009, 464 patients with ADHF were admitted to Yonsei Cardiovascular Hospital (Seoul, Republic of Korea). Among them, 256 patients were diagnosed as ND-ADHF and were investigated in this study. We defined ND-ADHF as “the first” presentation of having symptoms and showing signs of ADHF in patients who had no medical history of CHF before admission. The diagnosis of HF was made according to ACC/AHA 2005 guidelines.¹⁰ Admission routes were via either outpatient department (OPD) or emergency room (ER). Chronic kidney disease (CKD) was defined as a glomerular filtration rate (GFR) < 60 mL/min/1.73 m², according to the Modification of Diet in Renal Disease formula, or as requiring hemodialysis on a regular basis. All patients were managed by experienced cardiologists. Clinical outcomes including in-hospital mortality, re-hospitalization due to HF aggravation and cardiovascular (CV) mortality during follow-up period were investigated and compared between EPs and

NEPs. In-hospital mortality was defined as death from any cause which occurred during the index admission, and CV mortality was defined as death from refractory HF, myocardial infarction or stroke. Re-hospitalization was determined as an unplanned admission during follow-up period due to HF aggravation, myocardial infarction or stroke.

Echocardiographic measurements

Comprehensive echocardiographic evaluations were performed using commercially available equipment (Vivid 7, GE Vingmed ultrasound, Horten, Norway or Sonos 5500, Philips Medical System, Andover, Mass, USA) on all patients within 24 hours of admission. The left ventricular (LV) ejection fraction (EF) was determined using the modified Quinones method. The left atrial volume index (LAVI) was determined using the prolate ellipsoid formula as described previously.¹¹ Every study subject underwent pulsed-wave Doppler evaluation of mitral inflow and tissue Doppler image (TDI) and following variables were measured: early mitral inflow velocity (E), late mitral inflow velocity (A), and deceleration time (DT) of the E wave. Simultaneously, peak systolic mitral annulus velocity (S') and early diastolic mitral annulus velocity (E') were determined at the septal corner of the mitral annulus from the apical four-chamber view and E/E' was calculated. The mean of five measurements were analyzed. The index echocardiographic data were gathered and two experienced echocardiographers, who were unaware of patients' clinical data, performed a post-hoc analysis.

Laboratory measurements

At the time of admission, blood sample was acquired in all patients for routine chemistry test including N-terminal pro brain natriuretic peptide (NT-ProBNP). The blood samples for NT-proBNP were kept at the temperature of 4°C and analyzed using the electrochemiluminescence immunoassay method (Elecsys proBNP; Roche Diagnostics GmbH, Basel, Switzerland). Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease formula equation: $170 \times (\text{SCr})^{-0.999} \times (\text{age})^{-0.176} \times (\text{BUN})^{-0.170} \times (\text{albumin})^{0.318} \times 0.762$ (if female), where SCr is serum creatinine in mg/dL.

Statistical analysis

Continuous data are expressed as mean values \pm standard deviation (SD). Because the NT-proBNP distribution was positively skewed, we used log-transformed NT-proBNP

values in statistical analysis. The baseline characteristics of the two groups were compared using the unpaired Student *t*-test for continuous variables, and the Chi-square test for categorical variables. Kaplan-Meier tests were used to analyze clinical outcomes in the two groups. Statistical data were processed by SPSS (Window Release 13.0; SPSS Inc, Chicago, IL, USA). A two-tailed *p* value of < 0.05 was considered significant.

RESULTS

Clinical characteristics and laboratory findings

The initial clinical characteristics with intergroup comparison data are provided in Table 1. Female gender, diabetes mellitus (DM), previous stroke and hypertension were more common in EPs. Admission via ER was more frequent in NEPs. The mean body mass index of EPs was significantly lower than that of NEPs. The length of hospital stay was not significantly different between the two groups. The incidence of ADHF originating from ischemic heart disease was more prevalent in EPs. Significant differences were observed in eGFR, NT-proBNP, hemoglobin and high-sensitivity C-reactive protein (hsCRP) between EPs and NEPs ($p < 0.05$ for all). There was no significant difference in medications prescribed upon discharge between two groups.

Echocardiographic findings

Table 2 shows the initial echocardiographic parameters for enrolled patients with intergroup comparison data. Mean LVEF and LAVI were slightly higher in EPs than NEPs, but the differences between the two groups were statistically insignificant. However, E' and S' , which reflect the myocardial properties of relaxation and contraction respectively, were significantly lower in EPs as compared with those in NEPs. The mean DT of the E wave velocity was significantly longer in EPs than in NEPs. Additionally, E/E' , which reflects end-diastolic LV filling pressure (LVFP), was significantly higher in EPs compared with NEPs.

Clinical outcomes

Among the study population, in-hospital death occurred in 20 patients (10 EPs and 10 NEPs, time to death ranging from 1 day to 58 days). In-hospital mortality rates between EPs and NEPs were not significantly different (7.4% vs. 8.3%, $p = 0.820$). The mean follow-up period for the entire study population was 44.7 ± 14.5 months. There was no

difference in follow-up duration between EPs and NEPs (44.9 ± 14.6 months vs. 44.4 ± 14.5 months, $p = 0.799$). Interestingly, there were no significant differences in re-hospitalization rate (31.1% vs. 32.2%, $p = 0.922$) and CV mortality (14.1% vs. 11.6%, $p = 0.567$) between EPs and NEPs during follow-up (Figs. 1 and 2).

DISCUSSION

The principal findings of this study were that 1) female gender, DM, previous stroke and hypertension were more common in EPs; 2) less dilated LV with higher LVFP was noted in EPs; 3) clinical outcomes, including in-hospital mortality, re-hospitalization and CV mortality, were similar between the two groups during follow-up.

HF is primarily a disease of the elderly. Approximately 80% of patients hospitalized with ADHF are 65 years old or older.^{7,12} However, there is not enough data to clarify the clinical and echocardiographic characteristics of ADHF diagnosed for the first time in the elderly. The optimal therapeutic strategies for those EPs also remain to be determined.¹³ The results of the present study tell us that initial clinical presentation and echocardiographic findings of EPs with ND-ADHF may be different from those of NEPs. These factors should thus be considered when we treat EPs with ND-ADHF.

In this study, ND-ADHF of EPs was more common in women. EPs were also leaner than NEPs. Several studies have found a strong inverse relationship between indices of obesity and subsequent clinical prognosis for patients with HF.^{14,15} According to previous reports, prognosis of HF is particularly grave in EPs complicated by the presence of multiple co-morbidities.^{16,17} Our study group shows that DM, hypertension and previous stroke are more prevalent in EPs with ND-ADHF than NEPs. Moreover, renal function in EPs, assessed by estimated GFR (eGFR), was significantly poorer than in NEPs. Poor renal function itself is not only a poor prognostic factor for ADHF but also a crucial problem hindering proper management of HF, because controlling overloaded body fluid volume in ADHF patient is mandatory. In treatment of ADHF patients with renal dysfunction, drug response is not optimal and the need for renal replacement treatment is increased. Consequently, timely and effective treatment is difficult, and there are more chances of complications such as infection, hemorrhage and thrombosis in EPs with ND-ADHF.

Table 1. Intergroup Comparison of Clinical Characteristics and Laboratory Findings

	EPs (n = 135)	NEPs (n = 121)	<i>p</i> value
Demographic characteristics			
Age (yrs)	74.0 ± 6.9	50.6 ± 10.8	< 0.001*
Sex (male : female)	58 : 77	86 : 35	< 0.001*
BMI (at admission) (kg/m ²)	22.3 ± 4.5	24.0 ± 4.4	0.003*
ER admission (n, %)	72 (53)	100 (83)	0.016*
LOS (days)	14.6 ± 34.8	11.7 ± 17.8	0.400
Etiology of ADHF			0.015*
Idiopathic DCMP (n, %)	33 (24)	44 (36)	0.045*
Valvular (n, %)	20 (16)	18 (15)	0.843
Ischemic (n, %)	55 (41)	27 (22)	0.002*
Hypertensive (n, %)	11 (8)	8 (7)	0.640
Others (n, %)	15 (11)	24 (20)	0.078
DM (n, %)	45 (33)	26 (21)	0.035*
Hypertension (n, %)	76 (56)	51 (42)	0.024*
Dyslipidemia (n, %)	11 (8)	12 (10)	0.621
CKD (n, %)	36 (27)	21 (17)	0.074
Previous stroke (n, %)	22 (16)	9 (7)	0.030*
Previous myocardial infarction (n, %)	33 (24)	28 (23)	0.087
Atrial fibrillation (n, %)	61 (45)	45 (37)	0.195
Laboratory findings			
eGFR (mL/min/1.73m ²)	54.8 ± 24.3	69.2 ± 30.7	0.002*
NT-proBNP (pg/mL)	10,538.2 ± 109,42.3	6,771.0 ± 8,964.7	0.007*
Ln (NT-proBNP)	8.6 ± 1.4	8.0 ± 1.5	0.001*
Hemoglobin (g/dL)	12.3 ± 2.1	13.6 ± 2.3	0.001*
Homocysteine (μmol/L)	17.9 ± 8.3	15.3 ± 7.5	0.302
High sensitive C-reactive protein (mg/L)	28.5 ± 46.9	7.6 ± 11.6	0.001*
BUN (mg/dL)	24.9 ± 13.3	23.2 ± 16.4	0.351
Creatinine (mg/dL)	1.66 ± 1.82	1.80 ± 2.46	0.596
Glucose (mg/dL)	163.1 ± 107.6	143.0 ± 74.1	0.179
Uric acid (mg/dL)	6.2 ± 2.3	6.7 ± 2.5	0.328
Cholesterol (mg/dL)	148.3 ± 38.2	158.4 ± 40.9	0.187
Triglyceride (mg/dL)	94.4 ± 37.9	118.0 ± 69.9	0.152
HDL-cholesterol (mg/dL)	39.7 ± 6.7	39.6 ± 12.4	0.976
LDL-cholesterol (mg/dL)	98.5 ± 33.6	99.9 ± 34.7	0.871
Albumin (mg/dL)	3.8 ± 0.5	4.0 ± 0.5	0.116
Medications at discharge			
Antiplatelet agents (n, %)	75 (56)	65 (54)	0.438
Anticoagulants (n, %)	40 (30)	42 (35)	0.556
Diuretics (n, %)	101 (75)	89 (74)	0.314
ACEis (n, %)	67 (50)	60 (50)	0.666
ARBs (n, %)	32 (24)	25 (21)	0.416
Beta-blockers (n, %)	57 (42)	51 (42)	0.708
Calcium channel blockers (n, %)	22 (16)	32 (26)	0.075
Digitalis (n, %)	55 (41)	50 (41)	0.796
Nitrates (n, %)	39 (29)	37 (31)	0.981
Statins (n, %)	44 (33)	43 (36)	0.843

EPs, elderly patients; NEPs, non-elderly patients; BMI, body mass index; ER, emergency room; LOS, length of hospital stay; ADHF, acute decompensated heart failure; DCMP, dilated cardiomyopathy; DM, diabetes mellitus; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro B-type natriuretic peptide; BUN, blood urea nitrogen; HDL, high density lipoprotein; LDL, low density lipoprotein; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

**p* < 0.05.

Table 2. Intergroup Comparison of Echocardiographic Parameters

	EPs	NEPs	<i>p</i> value
LVEF (%)	34.5 ± 14.7	32.0 ± 15.9	0.208
LVEDD (mm)	57.6 ± 11.3	62.0 ± 10.9	0.003*
LVESD (mm)	48.1 ± 12.1	52.1 ± 12.7	0.014*
IVSD (mm)	10.1 ± 5.4	9.4 ± 2.2	0.215
PWD (mm)	9.6 ± 1.8	9.4 ± 2.3	0.652
LAVI (ml/m ²)	52.0 ± 26.7	50.6 ± 31.4	0.731
E (cm/sec)	78.0 ± 26.1	86.4 ± 32.7	0.058
A (cm/sec)	38.6 ± 23.3	58.1 ± 24.6	0.313
DT (msec)	171.2 ± 48.9	150.1 ± 52.0	0.008*
S' (cm/sec)	4.2 ± 1.5	4.7 ± 1.7	0.036*
E' (cm/sec)	4.0 ± 1.3	5.2 ± 1.9	< 0.001*
A' (cm/sec)	5.9 ± 1.9	5.8 ± 2.2	0.830
E/E'	21.2 ± 9.4	18.0 ± 8.9	0.025*

LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; IVSD, interventricular septal dimension; PWD, posterior wall dimension; LAVI, left atrial volume index; E, peak velocity of early diastolic filling; A, peak velocity of late filling, DT, deceleration time of the E-wave velocity; S', peak systolic mitral annular velocity; E', early diastolic mitral annular velocity; A', late diastolic mitral annular velocity; E/E', early mitral inflow velocity to early diastolic mitral annular velocity ratio.

**p* < 0.05.

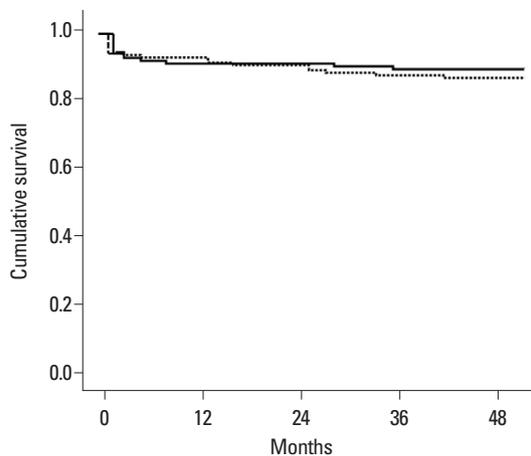


Fig. 1. Kaplan-Meier event-free survival curve for re-hospitalization due to heart failure aggravation.

Furthermore, EPs were more anemic and had significantly higher levels of hsCRP. Anemia and higher hsCRP are known to be ominous prognostic factors for HF. High hsCRP levels suggest that there could have been other co-morbid conditions such as inflammatory diseases in EPs. Plasma NT-proBNP levels were also much higher in EPs. Both NT-proBNP and BNP levels are known to increase with aging. Therefore, when we use NT-proBNP or BNP levels to diagnose CHF, age-dependent cutoff points should be considered. Plasma NT-proBNP level has been shown to be a biomarker for predicting LVFP in patients with HF.¹⁸ Although there are several limitations in the NT-proBNP based prediction of elevated LVFP, NT-proBNP levels have been considered a stan-

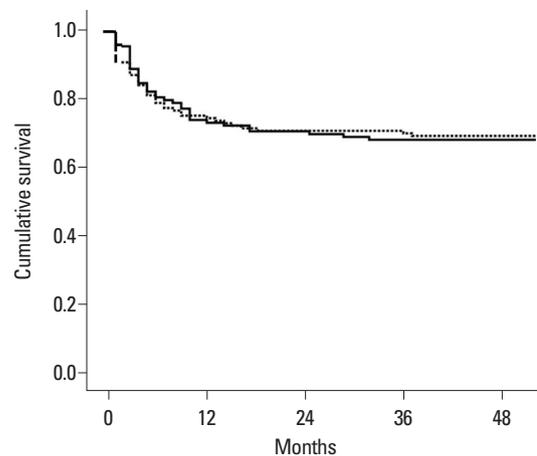


Fig. 2. Kaplan-Meier event-free survival curve for cardiovascular mortality.

dard biomarker for diagnosis and assessment of severity of HF. A significantly higher level of NT-proBNP in EPs suggests that EPs with ND-ADHF present a higher initial LVFP, which in turn indicates a poorer prognosis.¹⁹

The echocardiographic findings were also meaningful. Although the LVEF was not different, EPs had fewer dilated LV chambers than NEPs. E/E' was significantly higher and myocardial velocities including E' and S' were significantly lower in EPs than in NEPs. Previous studies showed that noninvasive reliable echocardiographic parameters of E/E' were positively correlated with invasive LVFP. These results mean that elevated LVFP is more problematic in EPs with ND-ADHF, as compared with NEPs.

Interestingly, our study showed no differences in in-hospital mortality, re-hospitalization and CV mortality between EPs and NEPs during follow-up. Our findings differ from previous knowledge regarding EPs with CHF. These results may be due to the small sample size of our study, but we suggest that our study provides information to important to understanding clinical features of EPs with ND-ADHF. In our opinion, age itself might not be a poor prognostic factor for CV mortality in patients with ND-ADHF. We think further studies should be performed regarding the long-term prognosis of ND-ADHF in EPs.

This study has the following limitations: first, it was conducted with a small sample population. Thus, only limited data analysis was possible, and we cannot exclude the possibility that the small sample size might be the cause of the unexpectedly favorable prognosis for EPs with ND-ADHF in this study. Second, our study was a single center retrospective investigation, so our analysis was limited to “selected” patients. Finally, we used a noninvasive echocardiographic parameter, E/E’, for the estimation of LVFP. We cannot neglect the discrepancy between E/E’ and direct-measured LVFP. Moreover, direct comparison of E/E’ between EPs and NEPs might be limited, because E/E’ is known to decrease normally with age.

In conclusion, EPs with ND-ADHF have different clinical and echocardiographic parameters when compared with NEPs. Therefore, these characteristic findings can be taken into account when we initially manage EPs with ND-ADHF. The clinical outcomes of EPs with ND-ADHF may not be more unfavorable when compared with those of NEPs. Further studies are required to uncover the long-term prognosis for ADHF and proper management strategies of EPs with ND-ADHF.

ACKNOWLEDGEMENTS

This study was supported by a grant of the Korean Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A080396).

REFERENCES

- Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM. Spectrum of heart failure in older patients: results from the National Heart Failure project. *Am Heart J* 2002;143:412-7.
- Miani D, Fresco C, Lucci D, Albanese MC, Gonzini L, Fioretti PM, et al. Clinical characteristics, management, and prognosis of octogenarians with acute heart failure admitted to cardiology wards: results from the Italian Survey on Acute Heart Failure. *Am Heart J* 2009;158:126-32.
- Fonarow GC. Epidemiology and risk stratification in acute heart failure. *Am Heart J* 2008;155:200-7.
- Coats AJ. Is preventive medicine responsible for the increasing prevalence of heart failure? *Lancet* 1998;352 Suppl 1:SI39-41.
- Heiat A, Gross CP, Krumholz HM. Representation of the elderly, women, and minorities in heart failure clinical trials. *Arch Intern Med* 2002;162:1682-8.
- Kannel WB. Epidemiology and prevention of cardiac failure: Framingham Study insights. *Eur Heart J* 1987;8 Suppl F:23-6.
- Kannel WB, Belanger AJ. Epidemiology of heart failure. *Am Heart J* 1991;121:951-7.
- Gambassi G, Forman DE, Lapane KL, Mor V, Sgadari A, Lipsitz LA, et al. Management of heart failure among very old persons living in long-term care: has the voice of trials spread? The SAGE Study Group. *Am Heart J* 2000;139:85-93.
- McMurray JJ, Pfeffer MA. Heart failure. *Lancet* 2005;365:1877-89.
- Hunt SA; American College of Cardiology; American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). 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 (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol* 2005;46:e1-82.
- Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pelliikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;18:1440-63.
- Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J* 1999;137:352-60.
- Parmley WW. Do we practice geriatric cardiology? *J Am Coll Cardiol* 1997;29:217-8.
- Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol* 2009;53:1925-32.
- Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;38:789-95.
- Mahjoub H, Rusinaru D, Soulière V, Durier C, Peltier M, Tribouilloy C. Long-term survival in patients older than 80 years hospitalized for heart failure. A 5-year prospective study. *Eur J Heart Fail* 2008;10:78-84.
- Lien CT, Gillespie ND, Struthers AD, McMurdo ME. Heart failure in frail elderly patients: diagnostic difficulties, co-morbidities, polypharmacy and treatment dilemmas. *Eur J Heart Fail* 2002;4:91-8.
- Daniels LB, Maisel AS. Natriuretic peptides. *J Am Coll Cardiol* 2007;50:2357-68.
- Kubler P, Jankowska EA, Majda J, Reczuch K, Banasiak W, Ponikowski P. Lack of decrease in plasma N-terminal pro-brain natriuretic peptide identifies acute heart failure patients with very poor outcome. *Int J Cardiol* 2008;129:373-8.