The aim of the present study was to investigate whether vitamin D supplementation could improve biochemical findings and functional capacity of patients with heart failure (HF). One hundred patients with New York Heart Association (NYHA) class I through III HF were included in this prospective study and their 25-hydroxyvitamin D levels were evaluated. Only 6% of the participants had a sufficient serum concentration of 25(OH)D >30 nmol/L. Patients with insufficient or deficient serum levels of 25(OH)D (<30 ng/mL and <20 ng/mL, respectively) received oral vitamin D₃ (cholecalciferol) for a total period of 4 months. Vitamin D supplementation increased mean serum concentration of 25(OH)D from 12.63±7.60 nmol/L to 54.49±18.01 nmol/L (P<.001). After vitamin D supplementation, the serum level of pro-brain natriuretic peptide markedly decreased (P<.001). Cholecalciferol significantly decreased high-sensitivity C-reactive protein level (P<.001). Restoration of serum 25(OH)D level was also associated with substantial improvement in NYHA class (P<.001) and 6-minute walk distance (P<.001).

Heart failure (HF) is an increasingly prevalent health problem affecting more than 15 million of patients worldwide. It is a major source of morbidity and mortality in elderly populations. It can be a debilitating syndrome that leads to significant functional limitations. Despite the advances in understanding the pathophysiology and treatment, it still has a poor prognosis. Only 35% of patients will survive within 5 years of diagnosis.

Vitamin D is a hormone that is necessary for bone and muscle health. However, it does not merely act on the calcium-phosphorus metabolism, and extraskeletal effects of vitamin D have been assumed. Limited dietary intake or skin synthesis are two important factors contributing to vitamin D deficiency. In some reports, a prevalence as high as 50% of the US adult population are vitamin D deficient. Vitamin D deficiency may be of particular importance in patients with HF, as a growing body of studies has found it to be more prevalent in patients with congestive HF. Accumulating evidence suggests that vitamin D deficiency in HF is not a negligible laboratory finding and there may be an intense association between these two common clinical entities. It has been shown that patients with congestive HF (CHF) had 34% lower 25(OH)D levels compared with controls. In some studies, emphasis has been given to the possible causative role of vitamin D in HF. Moreover, it was hypothesized that in patients with HF, vitamin D supplementation may reduce disease progression and symptom severity through suppression of the renin-angiotensin-aldosterone system and parathyroid hormone, down-regulation of inflammatory mediators, suppression of cardiac remodeling, promotion of cell growth and differentiation, reduction of blood pressure, and improvement in muscle strength. As a result, numbers of studies were designed to evaluate the beneficial or detrimental effects of vitamin D on HF. However, data are still lacking regarding the precise effects of vitamin D supplementation on laboratory parameters as well as functional capacities of HF patients. Therefore, the present study was designed to investigate whether vitamin D restoration could improve biochemical and functional parameters of CHF.

MATERIALS AND METHODS

Participants
One hundred consecutive patients with the diagnosis of CHF according to the European Society of Cardiology guidelines aged 15 years and older who presented to the Heart Failure and Transplant Clinic of Rajaei Cardiovascular, Medical and Research Center, a tertiary center for cardiovascular diseases in Tehran, Iran, during September 2010 and February 2012 were enrolled in this prospective study. All patients have been on optimal medical treatment of diuretics and neurohormonal blockers according to latest guidelines on HF management for at least the 3
Heart Failure and Cardiac Rehabilitation

Cardiac Examination
The severity of HF was assessed by a thorough physical examination. The NYHA function class of all patients was determined by the same investigator by evaluating each patient at rest, dressing, walking, and climbing the stairs. NYHA scores range from I (no symptoms of HF) to IV (symptoms at rest).20

Physical Performance Assessment
Physical performance of patients was assessed using the 6-minute walk test (6MWT) according to the protocol of Guyatt and colleagues.21

Biochemical Measurements
Blood samples were collected in the morning after an overnight fast and immediately processed on the same day. Serum calcium and phosphorus were measured by colorimetric method. PTH was measured using immunoassay (Immulet 1000; Siemens Medical Solutions Diagnostics, Los Angeles, CA) with an average intra-assay variability of 3.2%. Serum 25 (OH) D concentration was by enzyme immunoassay (DiaSorin, Saluggia (Vercelli), Italy). The intra-assay and inter-assay coefficients of variations (CVs) were 4.5% and 8.5%, respectively. Serum pro–brain natriuretic peptide (proBNP) levels were determined by enzyme immunoassay (Siemens Healthcare Diagnostic Inc, Elkhart, IN), with intra-assay and inter-assay CVs of 6% and 7.7%, respectively. Participants were classified into 3 categories on the basis of serum 25 (OH) D levels. Patients with 25 (OH) D levels of 30 ng/mL were classified as “normal,” while levels of 20 to 29.9 ng/mL were considered “insufficient,” and levels of <20 ng/mL were “deficient.”

Echocardiographic Examination
All echocardiographic data were obtained and processed by the same echocardiographer. Echocardiography was performed using a Vivid 7 device (GE Medical System, Milwaukee, WI) with a 3-MHz variable frequency harmonic phased array transducer. Measurement of left ventricular end-diastolic dimension (EDD) was performed at the parasternal long-axis view by M-mode echocardiography. Left ventricular end-systolic volume (ESV) and left ventricular ejection fraction (EF) were measured by modified Simpson’s method.

Vitamin D Supplementation
Patients with insufficient or deficient levels of 25 (OH) D were administered oral vitamin D3 (cholecalciferol) for a period of 4 months. The treatment regimen included 50,000 IU every week for 8 consecutive weeks followed by 50,000 IU every month for 2 consecutive months. Afterward, all patients, including those with normal baseline 25 (OH) D, were assessed again.

Statistical Analysis
All analyses were conducted by Statistical Package for Social Sciences software, version 19 (SPSS Inc, Chicago, IL). All data were initially analyzed using the Kolmogorov-Smirnov test to assess for normality. Categorical variables are presented as numbers and percentages and quantitative variables as mean±standard deviation. Categorical data were compared by chi-square test and quantitative variables by Student t test, Mann-Whitney test, the Kruskal-Wallis test, as appropriate. For comparative analysis of quantitative variables between vitamin D subgroups or NYHA functional classes, one-way ANOVA was used. Relationships were assessed using Pearson, Spearman, or Kendall tests depending on their distribution. Changes in all of the outcome measures were normally distributed and were analyzed using 2-sample Student t test. All P values were two-tailed and P<.05 was considered statistically significant.

RESULTS
Patient Characteristics
One hundred patients, including 73 (73%) men and 27 (27%) women, were enrolled in the study. The mean age of the cohort was 45.25±15.53 years. The demographic characteristics of the patients are shown in Table I.

Cardiac Characteristics
Nonischemic cardiomyopathy (73%) was the main cause of CHF in our study population. At the time of clinical evaluation, the percentages of NYHA class I, II, and III were 3%, 45%, and 52%, respectively.

Physical Performance Characteristics
Table II shows the physical performance characteristics of the study group. The mean 6MWT was 361±77 m. Subgroups of 25 (OH) D did not significantly differ among the different NYHA class groups.

preceding months. Moreover, patients were kept on the same medical regimen (including the type and dose of the medications) during the study period. Patients were excluded if they had hypercalcemia; nephrolithiasis; sarcoidosis; hemotoneal or peritoneal dialysis and/or serum creatinine concentration of >2 mg/dL; myocardial infarction in the preceding 6 months; and intake of supplements containing vitamin D and/or calcium, corticosteroids, parathyroid hormone (PTH), androgen, or estrogen. Patients with New York Heart Association (NYHA) class IV and patients with any exacerbations of HF symptoms during the last 3 months were also excluded.

The study was reviewed and approved by the institutional review board at the Tehran University of Medical Sciences and written informed consent was obtained from all participants. It should be noted that the present study complies with the Declaration of Helsinki.
The baseline serum PTH level was significantly correlated with higher NYHA functional class (r=0.31, P<0.01). Serum calcium level was inversely correlated with NYHA class (r=-0.23, P=0.01). Serum level of proBNP level was inversely associated with NYHA class and serum level of proBNP (r=-0.37, P<0.001). Serum calcium level was inversely correlated with proBNP (r=-0.22, P=0.02) (Figure 1).

High-sensitivity C-reactive protein (hs-CRP) was correlated with serum proBNP level (r=0.22, P=0.02). Serum level of proBNP was also inversely associated with 6MWT (r=-0.27, P=0.05). ProBNP and 6MWT were significantly different among CHF patients with NYHA class I to III (both P<0.001).

**Associations of Vitamin D With HF**

It is worth noting that the differences of mean serum concentrations of hs-CRP among patients with various 25 (OH) D subgroups were inconspicuous (P=11). The concentrations of proBNP were not significantly different among CHF patients with various vitamin D profiles (mean values: 1125.16 ng/L for patients with normal 25 (OH) D level, 2718 ng/L for patients with insufficient 25 (OH) D level, and 2626.80 ng/L for patients with deficiency of 25 (OH) D level; P=0.08). Furthermore, baseline 25 (OH) D had no significant association with NYHA functional class, proBNP level, or 6MWT at the time of enrollment to the study (all P>.05).

**Associations of PTH With HF**

The baseline serum PTH level was significantly associated with higher NYHA class and serum proBNP level (r=0.20, P=0.04 and r=0.28, P=0.004, respectively). Moreover, the baseline serum PTH level was negatively correlated with 6MWT (r=-0.31, P=0.001) (Figure 2). Hyperparathyroidism (PTH >87 ng/L) was associated with higher NYHA functional class (r=0.23, P=0.01).

**Effects of Vitamin D Supplementation**

After supplementation in patients with insufficient or deficient levels of 25 (OH) D, mean concentration of 25 (OH) D increased by 41.86 nmol/L. Vitamin D supplementation decreased mean serum PTH concentrations by 36.73 ng/L. Moreover, a 1.44-mg/dL decrease in mean serum calcium along with a 394±61 m for the normal group, 353±62 m for the insufficient group, and 360±81 m for the deficient group, P=0.48).

**Biochemical Characteristics**

The biochemical characteristics of the study participants according to 25 (OH) D subgroups are illustrated in Table III. Among 100 CHF patients, 76% had vitamin D insufficiency or deficiency at the time of enrollment. Only 6% of the participants in the study had a sufficient serum concentration of 25 (OH) D >30 nmol/L. Serum PTH was significantly correlated with 25 (OH) D (r=0.21, P=0.03). No significant differences were present regarding the frequency of 25 (OH) D subgroups or concentrations of 25 (OH) D, calcium, phosphorus, and proBNP in men and women (all P>.05). A significant correlation was seen between the NYHA functional class and serum level of proBNP (r=0.37, P<0.001). Serum calcium level was inversely correlated with proBNP (r=-0.22, P=0.02) (Figure 1).

High-sensitivity C-reactive protein (hs-CRP) was correlated with serum proBNP level (r=0.22, P=0.02). Serum level of proBNP was also inversely associated with 6MWT (r=-0.27, P=0.05). ProBNP and 6MWT were significantly different among CHF patients with NYHA class I to III (both P<0.001).
0.13-mg/dL increase in mean serum phosphorus levels was seen. All of these changes in biochemical parameters, including 25(OH) D, calcium, phosphate, and parathyroid hormone were considered statistically significant (all \( P < .001 \)). During 12 weeks of medical treatment with vitamin D, mean NYHA functional class in the study population improved significantly (\( P < .001 \)).

Furthermore, a reduction of 827.32 pg/mL was seen in the mean serum concentration of proBNP hormone (\( P < .001 \)). Vitamin D supplementation also significantly improved 6MWT (\( P < .001 \)). Compared with baseline values, a statistically significant decline was seen in serum level of hs-CRP, an inflammatory marker in HF (\( P < .001 \)). Comprehensive data regarding the changes in the aforementioned variables is provided in Table IV. Vitamin D supplementation also improved a number of echocardiographic measures, as shown in Table IV.

### Patients With Sufficient Baseline Serum Level of 25(OH) Vitamin D

Data for the untreated group are depicted in Table V and it is noteworthy to mention that this “vitamin D sufficient” group was so small in number (6 patients) that the results could not be brought up as a comparison to the treated group. However, considering the standard “neurohormonal blockade escalation” strategy (up titration of \( \beta \)-blockers, angiotensin-converting enzyme inhibitors, and mineralocorticoid receptor antagonists) in this untreated group, their merely unchanged clinical status might be of importance.

### Safety Measures

None of the participants in the study experienced an increase in serum creatinine >50% from baseline. Moreover, none of the patients exhibited clinical features of vitamin D intoxication during the study period. Hypercalcemia was mild and asymptomatic in all detected cases and did not result in the need for discontinuation of therapy.

### DISCUSSION

This is one of few studies, at least to our knowledge, that evaluated the efficacy of vitamin D supplementation in an HF population. The main finding of the current investigation is that 12 weeks of administration of oral vitamin D\(_3\) to HF patients with insufficient or deficient levels of serum vitamin D markedly improves their physical performance and the laboratory parameters of HF.

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**TABLE III. Biochemical Characteristics of the Study Population According to 25(OH) D Concentrations**

<table>
<thead>
<tr>
<th></th>
<th>All (n=91)</th>
<th>Normal (n=6)</th>
<th>Insufficient (n=18)</th>
<th>Deficient (n=76)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH, ng/L</td>
<td>106.89 ± 65.14</td>
<td>62.76 ± 18.19</td>
<td>91.69 ± 42.19</td>
<td>113.97 ± 70.10</td>
<td>.04*</td>
</tr>
<tr>
<td>Ca, mg/dL</td>
<td>9.60 ± 0.59</td>
<td>9.80 ± 0.67</td>
<td>9.81 ± 0.56</td>
<td>9.53 ± 0.58</td>
<td>.11</td>
</tr>
<tr>
<td>Ph, mg/dL</td>
<td>4.01 ± 0.62</td>
<td>4.05 ± 0.76</td>
<td>4.23 ± 0.47</td>
<td>3.95 ± 0.64</td>
<td>.07</td>
</tr>
<tr>
<td>25(OH) D, nmol/L</td>
<td>14.35 ± 10.88</td>
<td>24.20 ± 14.87</td>
<td>15.88 ± 7.89</td>
<td>17.08 ± 13.65</td>
<td>.11</td>
</tr>
<tr>
<td>hs-CRP, mg/dL</td>
<td>14.35 ± 10.88</td>
<td>41.33 ± 15.95</td>
<td>25.33 ± 2.39</td>
<td>9.64 ± 4.72</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

**Abbreviations: Ca, calcium; hs-CRP, high-sensitivity C reactive protein; Ph, phosphorus; PTH, parathyroid hormone.**

Data are presented as mean ± standard deviation.

*Statistically significant.

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**FIGURE 1.** Baseline pro–brain natriuretic peptide (proBNP) and calcium levels were inversely correlated (\( r = −0.22, P = .02 \)).

**FIGURE 2.** Baseline parathyroid hormone (PTH) was negatively correlated with six-minute walk test (6MWT) (\( r = −0.31, P = .001 \)).
### TABLE IV. Effects of Vitamin D Supplementation on Biochemical, Functional, and Echocardiographic Parameters in Patients With Insufficient or Deficient Levels of 25 (OH) D

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Deficient (n=76)</th>
<th>Insufficient (n=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, mg/dL</td>
<td>9.80±0.67</td>
<td>9.69±0.82</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>4.05±0.76</td>
<td>4.03±0.72</td>
</tr>
<tr>
<td>hs-CRP, mg/dL</td>
<td>24.20±14.87</td>
<td>20.09±12.03</td>
</tr>
<tr>
<td>proBNP, pg/mL</td>
<td>1125.16±696.62</td>
<td>1022.82±726.82</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>394±61</td>
<td>407±72</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.16±0.75</td>
<td>1.83±0.75</td>
</tr>
<tr>
<td>EF</td>
<td>21.66±13.66</td>
<td>23.02±10.74</td>
</tr>
<tr>
<td>EDD</td>
<td>103.33±32.21</td>
<td>139.11±29.46</td>
</tr>
<tr>
<td>ESV</td>
<td>5.88±0.62</td>
<td>6.26±0.46</td>
</tr>
<tr>
<td>E/E_m</td>
<td>9.66±2.58</td>
<td>9.36±1.83</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ca, calcium; E/E_m, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; EDD, end-diastolic dimension; EF, ejection fraction; ESV, end-systolic volume; NYHA, New York Heart Association; Ph, phosphorus; proBNP, pro-brain natriuretic peptide; 6MWT, 6-minute walk test.

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### TABLE V. The Changes in Biochemical, Functional and Echocardiographic Parameters in Patients With Sufficient Levels of 25 (OH) D During the Study Period

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>After 4 Months*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 (OH) D, nmol/L</td>
<td>41.33±15.95</td>
<td>47.72±13.82</td>
<td>.79</td>
</tr>
<tr>
<td>PTH, ng/L</td>
<td>62.76±18.19</td>
<td>69.62±13.27</td>
<td>.87</td>
</tr>
<tr>
<td>Ca, mg/dL</td>
<td>9.80±0.67</td>
<td>9.69±0.82</td>
<td>.48</td>
</tr>
<tr>
<td>Ph, mg/dL</td>
<td>4.05±0.76</td>
<td>4.03±0.72</td>
<td>.82</td>
</tr>
<tr>
<td>hs-CRP, mg/dL</td>
<td>24.20±14.87</td>
<td>20.09±12.03</td>
<td>.07</td>
</tr>
<tr>
<td>proBNP, pg/mL</td>
<td>1125.16±696.62</td>
<td>1022.82±726.82</td>
<td>.36</td>
</tr>
<tr>
<td>6MWT, m</td>
<td>394±61</td>
<td>407±72</td>
<td>.42</td>
</tr>
<tr>
<td>NYHA</td>
<td>2.16±0.75</td>
<td>1.83±0.75</td>
<td>.17</td>
</tr>
<tr>
<td>EF</td>
<td>21.66±13.66</td>
<td>23.02±10.74</td>
<td>.81</td>
</tr>
<tr>
<td>EDD</td>
<td>103.33±32.21</td>
<td>139.11±29.46</td>
<td>.62</td>
</tr>
<tr>
<td>ESV</td>
<td>5.88±0.62</td>
<td>6.26±0.46</td>
<td>.17</td>
</tr>
</tbody>
</table>

**Abbreviations:** Ca, calcium; E/E_m, ratio of early transmitral flow velocity to early diastolic mitral annulus velocity; EDD, end-diastolic dimension; EF, ejection fraction; ESV, end-systolic volume; NYHA, New York Heart Association; Ph, phosphorus; proBNP, pro-brain natriuretic peptide; 6MWT, 6-minute walk test.

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In previous studies it has been shown that restoration of serum vitamin D improves muscle strength and walking distance. However, little was known regarding the effects of vitamin D therapy on 6-minute walk distance in the HF population. In our study, vitamin D supplementation caused an improvement in exercise capacity of patients with HF, reflected as prolongation of 6MWT. This is in contrast to the previous report by Witham and colleagues, which showed that a regimen of 100,000 IU of ergocalciferol at 0 and 10 weeks did not significantly improve the 6-minute walk distance in 53 elderly patients with systolic HF.

A prospective double-blind randomized trial was conducted by Schleithoff and colleagues in 123 HF patients with NYHA class >II. They randomly assigned younger patients with HF to receive either a combination of vitamin D3 (cholecalciferol) at a dose of 2000 IU daily and calcium (500 mg daily) or calcium and placebo. After 9 months they assessed inflammatory cytokines, echocardiographic parameters, and overall survival. Their results showed that patients who received vitamin D did not show a significant reduction in tumor necrosis factor (TNF-α).

Although, in the patients treated with calcium alone, a significant (12% from baseline value) increase was seen in the concentration of TNF-α. On the other hand, interleukin 10 concentrations increased by 43% in the group treated with vitamin D while it did not change significantly in the other group. The results of this study shed light on the possible role of vitamin D.
supplementation in the reduction of the inflammatory state in patients with HF. Their findings also support the results of our investigation, which revealed that vitamin D therapy may suppress the inflammation process in HF, measured by hs-CRP. Although, Schleithoff and colleagues showed that the changes in CRP had no significant difference between patients treated with or without vitamin D. The significance of this controversy is questionable, however, and further investigations are needed to clarify the possible anti-inflammatory effects of vitamin D supplementation in HF.

Our results showed that vitamin D supplementation in HF patients led to a significant decline in the plasma concentration of proBNP. This finding concurs with the previous reports by Witham and colleagues in the study described above, which revealed a substantial fall in BNP level after 10 weeks of therapy with oral vitamin D2 supplementation. However, Schleithoff and colleagues believed that vitamin D supplementation could not significantly affect serum concentrations of natriuretic peptides.

It is also noteworthy that Witham and colleagues tried a 2-bolus administration of 100,000 U of ergocalciferol in contrast to the weekly regimen we applied, which might provide patients with more steady serum levels of vitamin D. Although Witham and colleagues believed that their treatment strategy would induce more than a 100% rise in 25-hydroxyvitamin D level at 10 weeks with a sustained level at 20 weeks, they failed to increase the average concentration of post-supplementation 25 (OH) D level to the sufficient level. Moreover, their study was conducted on the elderly population. As proposed by Levanit and Judd, vitamin D treatment may have unremarkable effects on HF in older patients. On the other hand, in the study by Schleithoff and colleagues, a concomitant supplementation of calcium was also carried out. It has been previously postulated that calcium treatment may adversely affect vascular health independent of vitamin D supplementation.

It has been shown previously that low circulating 25 (OH) D is associated with left ventricular dilatation and reduced function. Ameri and colleagues showed that patients with serum 25 (OH) D level <25 nmol/L had significantly higher left ventricular dimensions and volumes, as compared with patients with a 25 (OH) D level >25 nmol/L. However, because of the small number of patients with sufficient baseline vitamin D level (n=6), we could not make a comparison between our study groups in this regard. Other important finding of our study is that vitamin D therapy may affect ventricular function in a favorable pattern. We showed that patients with depleted serum 25 (OH) D levels had a significant increase in left ventricular EF after 4 months of vitamin D supplementation. The effect of vitamin D therapy on left ventricular ESV was also remarkable. Moreover, left ventricular end-diastolic dimension and E/Em were also notably altered toward favorable “reverse remodeling.” This may explain the rationale of the improvements in the clinical and functional parameters of HF after vitamin D supplementation. However, establishing the significance of these findings merits further studies with more detailed echocardiographic indices, which could confidently elucidate the effects of vitamin D on geometry and function of the failing hearts.

STUDY LIMITATIONS
There are several important strengths of this study. Firstly, using the described regimen for vitamin D supplementation, we could raise the average concentration of the vitamin D level in our study population to the optimum level. After supplementation, none of the patients had deficient levels of 25 (OH) D. It has been demonstrated that serum 25 (OH) D concentrations of >33 ng/mL and <90 ng/mL (80–225 nmol/L) may be adequate to restore vitamin D-dependent functions. Secondly, the present study included a younger study population and any intervention during the first years of the disease course may have more beneficial effects. Thirdly, we used vitamin D3 (cholecalciferol), which has a longer half-life and also results in greater peak levels of vitamin D.

The major limitations of the present study are the relatively small sample size and the lack of an arm of a placebo-treated control group. Results should be evaluated in comparison to a control group to minimize the effects of overlooked confounders.

CONCLUSIONS
The results of our study indicate that an appropriate strategy of vitamin D supplementation decreases the severity of HF, reflected in the reduction of serum proBNP. We also demonstrated that vitamin D causes a pronounced improvement in physical capacity of patients. Moreover, vitamin D was able to suppress the concentration of hs-CRP. Our data provide valuable evidence for the efficacy of vitamin D supplementation in the optimal management of HF.

Disclosure: None declared.

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20 Task Force for Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of European Society of Cardiology. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Eur Heart J. 2008;29:2388–442.


