Clinical Investigations

Selective Serotonin Reuptake Inhibitors Modify the Effect of β-Blockers on Long-Term Survival of Patients With End-Stage Heart Failure and Major Depression

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ABSTRACT

Background: Major depression (MD) is a key feature in heart failure (HF), and it is unclear whether common antidepressive medications interact with cardiovascular drugs used for the treatment of patients with MD and HF, affecting their efficacy. We examined the impact of MD on long-term survival of patients with end-stage severe HF. We also evaluated the interaction between antidepressive medication and β-blockers on the clinical outcome of these patients.

Methods and Results: The study population consisted of 250 patients with end-stage severe HF. Sixty-one percent of these patients suffered MD and were receiving selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), or tricyclic antidepressants (TCA). All patients were followed prospectively for 18 months. The primary end point was cardiovascular death. At baseline, patients with severe MD had higher serum interleukin 6 ($P < .05$) and soluble vascular cell adhesion molecule ($P < .01$). During the follow-up, 167 cardiovascular deaths were reported, and MD was 1 of the major predictors of cardiovascular death ($P = .031$), whereas treatment with angiotensin receptor inhibitors and statins were also important negative predictors of mortality ($P = .036$ and $P = .039$, respectively). Although β-blockers had a borderline nonsignificant effect on cardiovascular mortality in the overall population, they had a striking beneficial effect among those patients with major depression receiving SSRIs ($P = .006$), whereas they had a negative effect on mortality in those patients receiving SNRIs/TCAs ($P = .025$).

Conclusions: MD is an independent predictor of cardiovascular death in patients with end-stage HF. β-blockers are associated with lower cardiovascular mortality in patients with end-stage HF and depression only when they are combined with SSRIs. (*J Cardiac Fail 2008;14:456–464*)

Key Words: Heart failure, depression, inflammation, cardiovascular death, serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors.

Increasing evidence suggests that depression has direct effects on the cardiovascular system, because it has been associated with alterations of cardiac autonomic tone,[1] increased catecholamine levels,[2] and elevated inflammatory process.[3] Depression has been associated with elevated inflammatory markers with prognostic role in heart failure,[4] such as C-reactive protein, interleukin-6 (IL-6),[3] and tumor necrosis factor-α,[5] although it is still unclear whether depression is a result of the underlying disease state or whether it is causally implicated in the pathogenesis of heart failure syndrome. It has been reported that the prevalence of depression is >42% among patients with severe heart failure (New York Heart Association [NYHA] Class IV),[6] and it is associated with a 2-fold increase of the risk for cardiovascular death independently of the severity of the underlying heart failure.[6]

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Strong evidence suggests that β-blockers reduce the risk of cardiovascular death in patients with mild-to-moderate heart failure,[7–9] whereas there is also increasing evidence for their potential benefit in more severe disease states.[10] Indeed, despite the initial reports[12] suggesting that β-blockers do not improve clinical benefit in patients with severe heart failure, other large-scale clinical trials[10,11] demonstrated that β-blockers should be administered in this group of patients, with the exception of patients with decompensated heart failure. On the other hand, it is unknown whether patients with end-stage heart failure suffering from medically treated major depression have any benefit from β-blocker treatment. All antidepressants (such as selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], or tricyclic antidepressants [TCAs]) interfere with catecholamines recycling, and may have direct impact on α and β adrenergic stimulation in human myocardium.[13,14]

In the present study, we first examined the impact of major depression on the risk of cardiovascular death, in patients with end-stage, severe heart failure. Moreover, we examined the impact combined effects of β-blockers and antidepressive medication on the long-term survival in patients with end-stage severe heart failure.

Methods

Patients and Study Protocol

The study population consisted of 250 patients with systolic left ventricular dysfunction (left ventricular ejection fraction ≤40%, as evaluated visually by echocardiography) (Table 1). All patients belonged to the database of our department's clinic. At the time of recruitment, all patients had symptoms of dyspnea at minimal effort, unable to carry any daily activity, and were classified as NYHA IV. All the patients were discharged after optimization of their medical treatment, and improvement of their clinical symptoms at a lower NYHA class. Exclusion criteria were acute or chronic infectious or inflammatory diseases, recent myocardial infarction (<8 weeks) or active ischemia, hepatic or renal impairment (creatinine >2.5 mg/dL), and use of immunosuppressive drugs. Left ventricular ejection fraction was calculated by echocardiography, and blood samples were obtained after a 12-hour fasting period just before their discharge from the hospital.

Patients were discharged from the hospital after optimization of their medical treatment, and after an improvement of their clinical status (symptoms at the time of discharge from the hospital are listed in Table 2). The severity of depression was defined at the time of their discharge, and they were prospectively followed for 18 months. Most of these patients were hospitalized multiple times during the follow-up period.

Clinical Definitions

Cardiovascular death was defined according to the International Classification of Diseases-9, and included sudden death. Patients who died from other causes (n = 4) were censored at the date of death. Sudden death was defined as: 1) a witnessed death occurring within 60 minutes from the onset of new symptoms, unless a cause other than cardiac was obvious; 2) an unwitnessed death (<24 hours) in the absence of preexisting progressive circulatory failure or other causes of death; or 3) a death during attempted resuscitation. Deaths from end-stage heart failure were defined as those occurring in hospitals as a result of refractory progressive pump failure.

Table 1. Demographic Characteristics of the Participants

	No Depression	Depression
Number of participants	96	154
Age (y)	54.6 ± 12.7	59.6 ± 24.4†
Gender (males/females)	72/24	125/29
Type of heart failure (ischemic/nonischemic)	79/17	127/27
Ejection fraction (%)	32.6 ± 9.4	32.4 ± 15.9
Smoking, n (%)	47 (49%)	66 (42.9%)
Hypertension, n (%)	36 (37.5%)	56 (36.4%)
Hypercholesterolemia, n (%)	40 (41.7%)	44 (28.6%)*
Diabetes mellitus, n (%)	36 (37.5%)	48 (31.2%)
Systolic blood pressure (mm Hg)	113.8 ± 14.3	115.6 ± 27.0
Diastolic blood pressure (mm Hg)	67.2 ± 6.8	68.2 ± 12.6
Heart rate (beats/min)	74.1 ± 5.8	71.5 ± 11.1†
Cholesterol (mg/dl)	211.0 ± 43.1	209.0 ± 90.3
Triglycerides (mg/dL)	148.0 ± 70.5	135.0 ± 97.7
Glucose (mg/mL)	136.0 ± 52.9	141.0 ± 91.0
Urea (mg/dL)	60.7 ± 28.4	64.2 ± 66.6
Creatinine (mg/dL)	1.8 ± 5.7	1.7 ± 5.6
Uric acid (mg/dL)	6.5 ± 2.3	6.4 ± 4.2
BNP (pg/mL)	787 (433–1243)	873 (501–1457)
CRP (mg/mL)	9.59 (4.31–17.85)	7.1 (3.5–15.3)
Fibrinogen (mg/mL)	381.0 ± 136.8	357.0 ± 166.5
TNF-α (pg/mL)	4.4 (3.9–6.2)	4.2 (3.3–5.2)
Medication		
ACE inhibitor, n (%)	42 (43.8%)	68 (44.2%)
ARB, n (%)	26 (27.1%)	19 (12.3%)*
β-blockers, n (%)	45 (46.9%)	55 (35.7%)
Metoprolol (%)	20 (20.8%)	24 (15.6%)
Carvedilol (%)	22 (22.9%)	26 (16.9%)
Nebivolol (%)	3 (3.1%)	5 (3.2%)
Diuretics, n (%)	56 (58.3%)	79 (51.3%)
Nitrates, n (%)	57 (59.4%)	76 (49.4%)
Aspirin, n (%)	34 (35.4%)	55 (35.7%)
Warfarin, n (%)	27 (28.1%)	41 (26.6%)
Statins, n (%)	54 (56.3%)	73 (47.4%)
Allopurinol, n (%)	53 (55.2%)	74 (48.1%)
Antidepressants		
SSRIs, n (%)	—	120 (48%)
SNRI, n (%)	—	21 (8.4%)
TCA, n (%)	—	24 (9.6%)

Values expressed as mean ± SD or median (25th–75th percentile).

ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; SSRIs, selective serotonin reuptake inhibitors; SNRI, serotonin norepinephrine reuptake inhibitors; TCA, tricyclic antidepressants; TNF-α, tumor necrosis factor alpha; CRP, C-reactive protein.

*$P < .05$.

†$P < .01$ vs. no depression.

Assessment of the Severity of Depression

At baseline, the presence of depression (in those with history of depression) was confirmed and its severity was reevaluated by psychiatrist. The treatment regiments were prescribed by a psychiatrist before the patients' recruitment to the study, and the compliance of the patients to the treatment was confirmed by cross-checking the patients' medical prescription books (to make sure that a stable treatment was administered for at least the last 6 months).

The severity of depression was assessed by calculating the Depression Severity Score (DSS), as previously described in the Chronic Disease Self Management Program.[15] This score is