apy versus first-line RFA in patients with ≥2 symptomatic episodes of AFl and normal left atrial size. After a 21-month follow-up, only 36% of the patients receiving drugs in their study were in NSR versus 80% of patients who underwent RFA. They also reported very high (63%) rehospitalization rates for symptomatic AFl in the group that received medications compared with RFA group. RFA was not only superior in maintaining NSR, but also had a positive impact on quality of life and lower occurrence of atrial fibrillation. Compared with the present study, the enrolled patients in this study required a history of ≥2 episodes of AFl and normal left atrial size. Only 38% of patients had coronary artery disease; 54% had no structural heart disease and the ejection fraction was near normal (49 ± 3%). In our study, we enrolled patients after their first episode of AFl, 60% of patients had left atrial enlargement, almost 60% had coronary artery disease, and only 15% did not have structural heart disease. Thus, we studied a more diverse and "sicker" group of patients. Not surprisingly, we also observed a very high rehospitalization rate of 53%, with 11% of the patients rehospitalized twice due to the symptoms caused by recurrence of AFl. In the 18 patients who underwent RFA due to recurrent symptomatic AFl, none developed relapse. Thus, our data complement and support these previous observations. In particular, the drug therapy approach was distinctly unhelpful.

This was a retrospective, single-center study. Furthermore, patients were elderly with multiple co-morbidities, although the highest incidence of AFl in the general population derives from this group. Prophylactic drug therapy was not randomly assigned, but was prescribed at the discretion of the treating physician, and not all patients received potent antiarrhythmic drug regimens. Moreover, the inclusion of only symptomatic and electrocardiographically documented episodes of AFl may have led to underestimation of the timing of AFl recurrence.

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Brain Natriuretic Peptide Is Elevated in Outpatients With Atrial Fibrillation

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Brain natriuretic peptide (BNP) levels were measured in 72 outpatients with chronic atrial fibrillation (AF) and in 49 control patients without AF. BNP levels were significantly higher in patients with AF (median value 131 pg/ml) than without AF (median value 49 pg/ml; p <0.001), and remained significantly higher after controlling for demographic and clinical variables. ©2003 by Excerpta Medica, Inc.

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Brain natriuretic peptide (BNP) is a neurohormonal substance secreted predominantly in the left ventricle. This peptide has beneficial, compensatory actions to promote systemic arterial dilation, natriuresis, diuresis, and renin inhibition.[1] BNP has been shown to be elevated in patients with congestive heart failure and other cardiac conditions, including acute myocardial infarction, unstable angina, and left ventricular hypertrophy.[2–4] This recently discovered marker has been increasingly used in the diagnosis and treatment of congestive heart failure.[5] Recent data suggest that BNP levels may be associated with a poorer prognosis in patients with congestive heart failure and acute myocardial infarction.[6,7]

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Evidence regarding BNP levels in patients with atrial fibrillation (AF) has been conflicting and limited. Some reports have shown elevation in BNP lev-

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TABLE 1 Baseline Characteristics in the Two Study Groups

Variable	Chronic AF (n = 72)	Controls (n = 49)	p Value
Demographics			
Age (mean yrs)	70	69	0.50
Men	75%	69%	0.50
Comorbidities			
Hypertension	44%	51%	0.48
Coronary artery disease	15%	53%	<0.001
Diabetes	8%	8%	0.97
Medications			
ACE inhibitors	37%	32%	0.58
Aspirin	28%	73%	<0.001
β blockers	48%	51%	0.79
Calcium antagonists	49%	33%	0.08
Coumadin	88%	6%	<0.001
Digoxin	42%	2%	<0.001
Thiazide diuretics	25%	14%	0.17
Loop diuretics	12%	4%	0.19
Clinical data			
Heart rate (mean beats/min)	69	63	0.03
LVEF (mean %)	60	60	0.85
LA diameter (mean mm)	48	43	<0.003
No or trace MR	67%	82%	0.08
Mild MR	29%	11%	
Moderate to severe MR	4%	7%	
LV mass (mean g)	292	283	0.66

ACE = Angiotensin-converting enzyme; LA = left atrial; LVEF = left ventricular ejection fraction; MR = mitral regurgitation.

els in patients with AF compared with healthy subjects,[8] whereas others have found no independent association between BNP and AF in patients with left ventricular dysfunction.[9]

The aim of this study was to determine whether BNP is elevated in medically stable outpatients with chronic AF compared with outpatients in the same clinic without AF. A secondary study objective was to examine whether levels of BNP are associated with demographic and clinical variables in a sample of patients under study.

Consecutive patients with chronic AF who underwent medical care at an outpatient cardiology clinic were screened for the study. Patients were enrolled in the study if they had an unrelated blood sampling at the time of recruitment, if they consented to participate in the study, and if they met the predetermined inclusion and exclusion criteria. By definition, patients with chronic AF had 2 consecutive electrocardiograms in AF recorded over a 2-year period. Patients in the comparison group were recruited from the same clinic, did not have a history of AF based on review of medical records, and were in sinus rhythm at the time of study recruitment. Patients with prior heart failure, as well as patients who had symptoms of heart failure at the time of recruitment as determined by the patient's primary cardiologist, were excluded.

Information was collected from the review of outpatient medical records and included demographic data, history of comorbid conditions, current use of cardiac medications, and the results of cardiac tests, including electrocardiograms and echocardiograms. Twelve-lead electrocardiograms were analyzed to determine heart rate and presence of AF. Left ventricular ejection fraction was determined by a visual estimation method. Left ventricular mass was calculated by the Penn convention, as originally described by Devereux and Reichek.[10]

At the time of an unrelated blood sample collection, an additional 2 ml of blood was obtained for BNP measurement. Separated plasma using ethylenediaminetetraacetic acid as the anticoagulant was stored at −20°C until tested. The Triage BNP Test (Biosite, San Diego, California) was used for BNP measurements. This is a quantitative fluorescence immunoassay using murine monoclonal and polyclonal antibodies against BNP that has been validated in previous studies.[11]

Differences between patients with chronic AF and patients with sinus rhythm were examined using Fisher's test or analysis of variance tests for proportions and Student's *t* test for means of continuous variables. Univariable analysis was performed to examine associations between BNP and relevant clinical and demographic characteristics using simple linear regression. Multivariable linear regression analysis was performed with BNP as the principal outcome and predefined clinical characteristics, in addition to significant covariates from the univariable analysis, as predictors in the entire study sample.

The study sample included 72 patients with chronic AF and 49 control patients in sinus rhythm. The mean age of the study sample was 69 years and 73% were men. Comparison of baseline characteristics in the 2 groups is presented in Table 1. Patients in sinus rhythm were significantly more likely to have coronary artery disease, lower heart rates, smaller dimensions of left atrium, and to be treated with aspirin. Patients with chronic AF were more often prescribed coumadin and digoxin.

The median levels of BNP were significantly higher in patients with chronic AF than in patients in sinus rhythm (131 and 49 pg/ml, respectively; Figure 1). When both groups were stratified according to BNP levels, most patients with chronic AF fell into the upper 2 quartiles of BNP levels. In contrast, most patients with sinus rhythm were in the lower quartiles of BNP, with about 1/2 of control patients in the lowest BNP quartile.

In univariable analysis, older age, presence of chronic AF, larger left atrial size, presence of mitral regurgitation, and treatment with thiazide diuretics, β blockers, and coumadin were associated with higher BNP values in the total study sample. Multivariable analysis was performed with candidate variables, including presence of AF, predefined clinical characteristics, such as age, presence of coronary artery disease, left ventricular mass and ejection fraction, and

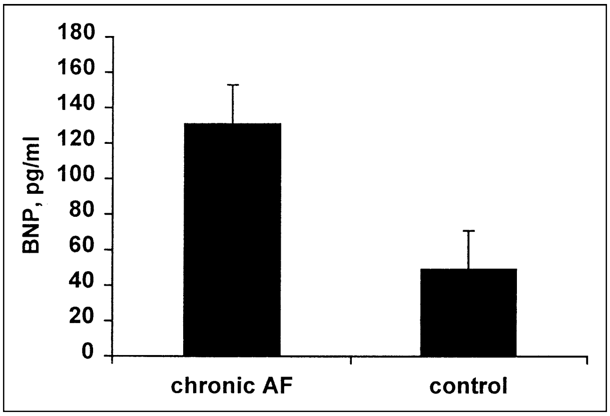

FIGURE 1. Median BNP levels in patients with and without AF.

TABLE 2 Association of Brain Natriuretic Peptide Levels and Clinical Predictors*			
Variable	Effect Estimate	SE	p Value
Age	3.8	1.1	0.001
β blockers	61.3	19.0	0.002
Presence of AF	75.8	22.3	0.001
Left atrial diameter	3.1	1.4	0.03

*Adjusted for coronary artery disease, left ventricular ejection fraction, left ventricular mass, presence of mitral regurgitation, and use of thiazide diuretics.

variables that were significant in univariable analysis. The final regression model showed that presence of chronic AF, older age, greater dimensions of left atrium, and the use of β blockers were independently predictive of higher BNP values (Table 2).

A similar linear regression model was performed in the subgroup of patients with chronic AF to determine the ability of clinical variables to predict higher BNP values in patients with AF. Similarly, older age, larger left atrial size, and the use of β blockers independently predicted higher BNP values in this patient group.

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To our knowledge, this is the first study that has shown BNP levels to be significantly elevated in male and female outpatients with chronic AF compared with patients in sinus rhythm. Our study recruited patients at a general cardiology clinic, not in a tertiary care setting. This makes the results of the study more applicable to the general population of patients with AF. Unlike most previous studies, our study also adjusted the levels of BNP in patients with and without AF for other clinical conditions that have previously been shown to affect BNP.

The causes of elevated BNP levels in patients with chronic AF are unclear. In patients with heart failure, the mechanism responsible for elevation of BNP has primarily been believed to be stretching of the left ventricular wall.[12] In patients with chronic AF, the higher levels of BNP may be associated with an unfavorable hemodynamic profile and altered left ventricular filling pattern resulting from the loss of atrial contraction. However, we did not specifically evaluate left ventricular diastolic function, and hemodynamic data were not available to allow us to make conclusions about the mechanism of BNP elevation in these patients.

In our study there was a strong independent association between BNP levels and treatment with β blockers. Higher BNP levels in patients treated with β blockers have been described previously, although the mechanism of that finding remains unclear.[13]

There are several clinical implications to our study. First, because BNP is increasingly used for diagnosis of heart failure, with the diagnostic cut-off limit often at 100 pg/ml, one should consider that there are other cardiac conditions not necessarily accompanied by heart failure that are also associated with increased BNP levels, among them chronic AF. Second, because the distribution of BNP levels differs among patients with chronic AF, from normal range to abnormally high levels, BNP may be a differential factor with prognostic abilities in this patient group. Previous studies have shown that patients with AF have higher mortality than their age- and gender-matched population controls, even when adjusted for risk factors; however, it has not been established how one can identify patients with AF who have poor prognoses.[14]

There are several possible limitations to the present study. Because we did not follow patients with AF from the onset of the diagnosis, we cannot establish the causal relation of AF to BNP. In addition, our control patients were recruited from the same outpatient cardiology clinic, and, therefore, had a higher prevalence of coronary disease than patients with chronic AF. However, we believe that if this contributed to any selection bias, the bias would be toward the null, because patients with coronary disease may have an elevated level of BNP. Furthermore, the association of chronic AF with high BNP levels remained after controlling for other clinical variables, including coronary disease.

Although our study shows an important association between BNP levels and the presence of AF, further research in this area is needed to confirm our findings in a larger population of patients with chronic AF. Studies are also needed to investigate the mechanisms responsible for elevated BNP levels in patients with chronic AF, and to determine whether the extent of BNP elevation has any prognostic significance in this group of patients.

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Usefulness of Implantable Loop Recorders in Office-Based Practice for Evaluation of Syncope in Patients With and Without Structural Heart Disease

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Early use of an implantable loop recorder for evaluating unexplained syncope in an office-based electrophysiology practice is an effective approach in patients with and without structural heart disease. Documentation of rhythm with an implantable loop recorder at the time of symptoms is possible in approximately 50% and 80% of patients in both groups after 1 and 2 years of follow-up, respectively. ©2003 by Excerpta Medica, Inc.

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Implantable loop recorders (ILRs) have recently become available.[1–3] These devices have a battery life of approximately 14 months and record and store a single-lead electrocardiogram when activated at the time of symptoms. Patients are provided with handheld activators to store the ambulatory electrocardiographic signal obtained for programmed intervals before and after an event. Some models have an automatic detection feature that will record rhythm strips in response to prespecified changes in heart rate. Studies of the use of the ILR in referral patients with recurrent, problematic syncope have been promising, with 1 early study showing a 68% diagnostic yield during a mean of 10.5 months of follow-up.[2] The use of ILRs in routine practice remains undefined. We retrospectively reviewed the use of ILRs in 2 university- and 2 office-based electrophysiology practices.

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The study group included 43 patients (26 women and 17 men, age 63 ± 15 years) with recurrent unexplained symptoms at 4 electrophysiology practices. Each received an ILR (Medtronic model 9525 Reveal or 9526 Reveal Plus, Minneapolis, Minnesota) between 1998 and 2001. Detection of P waves and QRS complexes was confirmed at implant. Devices were set for 3 patient-activated recordings, and, if available, automatic recordings for ≥3 seconds of asystole or ventricular rates >165 or <40 beats/min. Indications for insertion were syncope (38 patients), near-syncope (4 patients), and phantom defibrillator shocks (1 patient). Previous evaluations had been performed according to the referring physician's discretion. These included ambulatory electrocardiograms (n = 20), event recorders (n = 16), electrophysiologic studies (n = 17), stress tests (n = 19), tilt-table tests (n = 32), and cardiac catheterizations (n = 12). One patient had no diagnostic testing other than history, examination, and an electrocardiogram before ILR implantation. Twenty-nine patients had a diagnosis of structural heart disease, including hypertension (n = 15), coronary artery disease (n = 11), congestive heart failure (n = 6), valvular heart disease (n = 2), and right ventricular dysplasia (n = 1).

Follow-up concluded March 1, 2002, with all patients having ≥7 months of follow-up (mean 11.1 ± 10.4). All symptomatic events were noted and correlated with rhythm strips from the loop recorder. Asymptomatic arrhythmias recorded by the automatic detection function of the Reveal Plus model were also recorded. All patients were followed until the ILR was explanted or the follow-up period ended. Patients who had ≥1 symptomatic event that could be correlated with a rhythm strip were given a diagnosis based on that rhythm strip. Patients who had a normal rhythm during a symptomatic event continued follow-up as long as the ILR remained implanted. Our major findings concerned the overall diagnostic yield of the ILR,

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