Published in final edited form as:

Heart Rhythm. 2006 August ; 3(8): 881–886. doi:10.1016/j.hrthm.2006.05.010.

Lipid-lowering drug use is associated with reduced prevalence of atrial fibrillation in patients with left ventricular systolic dysfunction

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Abstract

BACKGROUND—Inflammation and oxidative stress have been implicated in the pathogenesis of atrial fibrillation (AF). Lipid-lowering drugs, particularly statins and fibrates, possess anti-inflammatory and antioxidant properties.

OBJECTIVES—The purpose of this study was to assess the impact of lipid-lowering drug use on AF prevalence in patients with reduced left ventricular ejection fraction (LVEF).

METHODS—Data were obtained from ADVANCESM, a multicenter registry of patients with reduced LVEF ($\leq 40\%$). Demographic, clinical, and echocardiographic parameters were collected from interviews and medical records. Medications, including lipid-lowering drugs, were recorded.

RESULTS—Of the 25,268 patients, 71.3% had hyperlipidemia, and 66.8% were prescribed lipid-lowering drugs. AF prevalence was 25.1% in patients taking lipid-lowering drugs compared with 32.6% in untreated hyperlipidemic patients and 32.8% in patients without hyperlipidemia ($P < .001$ for both comparisons). In multivariable analysis, lipid-lowering drug use remained significantly associated with reduced odds of AF (odds ratio [OR] 0.69, 95% confidence interval [CI] 0.64–0.74), and this effect was larger than that of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (OR 0.85, 95% CI 0.79–0.92) or β -blockers (OR 0.95, 95% CI 0.88–1.02). The beneficial impact of lipid-lowering drugs on AF risk was independent of their effects on the lipid profile. In patients in whom data on specific lipid-lowering drugs were available, 92% of the patients undergoing lipid-lowering therapy received statins, and 98% received statins and/or fibrates.

CONCLUSION—Use of lipid-lowering drugs in patients with reduced LVEF is associated with a significant reduction in the prevalence of AF independent of the lipid profile and other known arrhythmia risk factors. This effect is larger than that of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or β -blockers and may be the result of the antioxidant and anti-inflammatory effects of statins and fibrates.

Keywords

Atrial fibrillation; Lipid-lowering drugs; Prevention; Left ventricular dysfunction

Introduction

Atrial fibrillation (AF) worsens morbidity and mortality in patients with reduced left ventricular (LV) systolic function.^{1,2} Data suggest an association among inflammation, increased oxidative stress, and AF.

Examination of atrial tissue in patients with AF shows infiltration by inflammatory cells³ and increased levels of reactive oxygen species compared with controls.⁴ In addition, higher levels of serologic markers of inflammation, particularly C-reactive protein, have been associated with the presence of AF, an increased arrhythmia burden, and reduced success of cardioversion.^{5–7} Modulation of the inflammatory and oxidative milieu with corticosteroids or ascorbic acid has been shown to decrease the risk of AF after cardiac surgery and to reduce early recurrence after successful electrical cardioversion.^{8,9} Lipid-lowering drugs, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), have demonstrated pharmacologic properties independent of their beneficial effects on the lipid profile. These drugs possess anti-inflammatory and antioxidative properties, and they are increasingly being considered as novel antiarrhythmic drugs. Preliminary animal and human data suggest a protective effect of statins on AF risk. In the sterile pericarditis¹⁰ and the atrial rapid-pacing canine model of AF,¹¹ treatment with statins resulted in decreased inducibility and sustainability of the arrhythmia, with associated reductions in serologic and tissue markers of inflammation and decreased electrical remodeling (AF-induced shortening of the atrial action potential). In patients with lone AF, statin use reduced the risk of arrhythmia recurrence following cardioversion¹² and reduced the development of new AF in patients with coronary artery disease independent of cholesterol levels.¹³ Although encouraging, these human studies remain limited by their sample size and by the characteristics of the patients enrolled.

Emerging data also support a role for fibrates in the modulation of inflammation, through activation of the peroxisome proliferator-activated receptor α (PPAR $_{\alpha}$). This group of drugs reduces the serum levels and cellular expression of inflammatory mediators in animal models of hypertension and hyperlipidemia and decreases the risk of major cardiovascular events in humans with coronary artery disease.^{14–17}

In this study, we evaluated the effect of lipid-lowering drugs on AF prevalence in a cohort with reduced LV systolic function. Given the 5- to 10-fold higher risk of AF in this group compared with the general population,¹⁸ successful preventive strategies would have a large health impact.

Methods

Study population

Patients enrolled in the ADVANCENTSM registry (National Registry to Advance Heart Health) through September 30, 2004, were included in the study. ADVANCENTSM is a multicenter, observational registry designed to collect and report data on the histories, diagnostics, therapies, and interventions for patients with LV dysfunction (left ventricular ejection fraction [LVEF] $\leq 40\%$). This registry, designed to collect detailed medical and demographic information to assist physicians in identifying gaps in the care of patients with LV dysfunction, was sponsored by Guidant, Inc., and managed independently by REGISTRAT, Inc. At the time of data analysis, 25,268 patients from 106 centers in the United States had been enrolled.

Data from this cohort have been used for a prior study evaluating the relationship between stature and AF prevalence.¹⁹

Baseline data collection

At enrollment, all ADVANCENTSM participants were interviewed by medical personnel (physicians, nurse practitioners, and physician assistants), with additional data derived from review of medical records. Registry data contained information about age, gender, race, height, weight, LVEF, etiology of cardiomyopathy, New York Heart Association (NYHA) heart failure class, American College of Cardiology/American Heart Association heart failure stage, and coronary artery disease risk factors (tobacco smoking, hypertension, hyperlipidemia). Information regarding co-morbidities (diabetes, cancer, renal failure, anemia, cerebrovascular events, reactive airway disease, myocardial infarction, and syncope), medication use, and a variety of clinical events and interventions (angioplasty, coronary bypass surgery, pacemaker/defibrillator implant) also was gathered.

Atrial fibrillation

AF was identified through patient interviews, ECGs, and review of medical records. AF of any duration captured on ECGs or rhythm monitoring strips as well as from physician and/or patient reports of AF, at or prior to the time of enrollment in the ADVANCENTSM registry, were used for inclusion of patients in the AF group. In this cross-sectional study, any patient with AF either before or at the time of inclusion in the registry was classified as having a history of AF. At the time of completion of enrollment, 7,027 of 25,268 patients were found to have a history of AF.

Lipid-lowering drugs

Medication lists were obtained through patient interviews and review of medical records. Drugs belonging to the following groups were classified as lipid-lowering drugs: fibric-acid derivatives, bile-acid sequestrants, statins, ezetimibe, and niacin. The registry did not capture the specific lipid-lowering drug prescribed for each patient. These specific data were available only to us for the cohort recruited at Emory and Crawford Long Hospitals, through review of the heart failure database and hospital charts. The heart failure database is an electronic database that is updated by medical personnel at each patient visit to the heart failure clinic. Three hundred sixty-two patients, all recruited through the heart failure clinic, were enrolled in the ADVANCENTSM registry at our two hospitals.

Statistical analysis

Univariate analysis was first conducted to compare known risk factors for AF and arrhythmia prevalence. Chi-square statistics were used to evaluate the relationship between AF prevalence and dichotomous variables. In addition, contingency table analysis was used to compare the prevalence of AF in patients with no history of hyperlipidemia, those with hyperlipidemia not being treated, and those receiving lipid-lowering drugs. A logistic regression model was used to estimate odds ratios for AF and lipid-lowering drugs using SAS version 8.2. Using multivariable logistic regression models allowed for estimation of the odds of AF in relation to lipid-lowering drug use while controlling for the confounding effects of known arrhythmia risk factors. Age, height, LVEF, and body mass index were entered in the model as continuous variables. NYHA class was considered an ordinal variable. Gender, race, hypertension, diabetes, etiology of heart failure, and medication use (ACEI/ARB, β -blockers, lipid-lowering drugs, and Vaughn Williams class I and III antiarrhythmic drugs) were treated as dichotomous variables. In total, 23,478 patients (92.9% of the cohort) had complete data and were included in the multivariable regression analyses.

Results

The baseline characteristics of the 25,268 patients included in this study are detailed in our previous publication¹⁹ and are partially listed in Table 1. Mean patient age was 66.4 years. Coronary artery disease was the etiologic factor of the cardiomyopathy in 72.1% of subjects. Mean LVEF was 31%, with more than half of the patients in NYHA heart failure class II. Comorbid conditions included hypertension (72.4%), hyperlipidemia (71.3%), and diabetes mellitus (31.3%). The proportion of the population treated with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) was 81.7%, β -blockers in 79.1%, and lipid-lowering drugs in 66.8%.

Lipid-lowering agents and AF prevalence in univariate analysis

At or prior to enrollment, 7,027 patients were reported to have developed AF. The clinical characteristics associated with an increased AF prevalence included age ≥ 65 years, white race, male sex, valvular etiology of cardiomyopathy, and hypertension, with the latter failing to reach statistical significance. ACEI/ARB, β -blocker, and lipid-lowering drug use were associated with a significantly reduced prevalence of the arrhythmia compared with controls (26.7% vs 32.9%, 26.5% vs 33.5%, and 25.3% vs 33.1%, respectively; Table 2). This effect was most pronounced for lipid-lowering drugs, with a relative decrease in AF prevalence of 23.6% compared with 20.9% and 18.8% with β -blockers and ACEIs/ARBs, respectively. Interestingly, as previously reported,¹⁹ diabetes and coronary artery disease were associated with a significantly lower prevalence of AF in this population with reduced LV systolic function.

Lipid-lowering drugs and AF prevalence in multivariable regression analysis

We examined the relationship between lipid-lowering drug use and AF prevalence after adjusting for possible confounding factors. As shown in Figure 1 and Table 3, lipid-lowering drugs remained associated with a statistically significant reduction in arrhythmia prevalence (odds ratio [OR] 0.69, 95% confidence interval [CI] 0.64–0.74), an effect larger than that observed for ACEIs/ARBs (OR 0.85, 95% CI 0.79–0.92). Use of β -blockers showed a beneficial trend that did not reach statistical significance (OR 0.95, 95% CI 0.88–1.02).

The effects of other clinical characteristics on AF prevalence are shown in Figure 1. Increasing age, white race, hypertension, more advanced heart failure symptoms (NYHA class), and valvular cardiomyopathy were associated with a significantly higher prevalence of the arrhythmia. An opposite and statistically significant pattern was observed for diabetes, coronary artery disease, and LVEF.

Lipid-lowering drugs, AF prevalence, and lipid levels

To gain a better understanding of the mechanism of AF reduction resulting from lipid-lowering drugs, we evaluated the relationship between lipid levels and AF prevalence. As shown in Figure 2, the prevalence of the arrhythmia was significantly lower in patients taking lipid-lowering drugs (25.1%) compared with patients having hyperlipidemia who were not undergoing therapy (32.6%, $P < .001$) or with those not having hyperlipidemia (32.8%, $P < .001$). No statistically significant difference in the prevalence of AF between patients without hyperlipidemia and those with untreated hyperlipidemia were observed.

Using a multivariable logistic regression analysis to control for known AF risk factors, the odds ratios for the arrhythmia were higher for patients without a history of hyperlipidemia (OR 1.446, 95% CI 1.339–1.562) and for those with untreated hyperlipidemia (OR 1.338, 95% CI 1.183–1.514) compared with patients undergoing lipid-lowering therapy.

Lipid-lowering drugs in the Emory–Crawford Long cohort

To assess the particular classes of lipid-lowering drugs prescribed, we reviewed the records of patients enrolled in ADVANCENTSM at our two hospitals. This cohort consisted of 362 patients followed in the heart failure clinic. Of these, 159 (44%) patients were taking lipid-lowering drugs, with data on the specific agents used recorded for most of them (152 patients [96%]). Of the patients with a known lipid-lowering prescription, 140 were taking HMG-CoA reductase inhibitors (92%). This was the only class of drugs used in 113 patients. One hundred forty-nine patients (98% of those with a known lipid-lowering prescription) were taking statins and/or fibric-acid derivatives.

Discussion

In this study, we evaluated the impact of lipid-lowering drugs on AF prevalence in a large population of patients with reduced LV function. As expected for this cohort, there was a high prevalence of AF (28%) as well as hypertension, hyperlipidemia, and diabetes mellitus. We showed that the use of lipid-lowering drug was associated with a significant reduction in the odds of AF (31% relative reduction). This effect was more than that from ACEIs/ARBs or β -blockers and was independent of known AF risk factors. This result also was independent of the lipid profile, suggesting that the beneficial effect of lipid-lowering drugs is independent of their lipid-lowering properties.

The findings of this study suggest that lipid-lowering drugs may be useful for AF prevention in patients with LV systolic dysfunction. The development of AF in these patients is problematic because of an increased stroke risk, an overall increase in mortality, and the limited choice of safe and effective antiarrhythmic medications.

In our study, the beneficial effect of lipid-lowering drugs on AF risk was similar to that observed by Young-Xu et al.¹³ In a smaller cohort of patients with coronary artery disease and preserved LVEF, statin use resulted in an approximately 50% reduction in AF risk that seemed independent of its effect on the lipid profile. There are, however, important differences between the clinical characteristics and the medications used in the two populations. In our study, only patients with reduced LVEF were included, and the population had a high prevalence of AF risk factors, as reflected in the high prevalence of the arrhythmia. These factors, along with a higher rate of use of ACEIs/ARBs (65.6% vs 16.0%) and the inclusion of non-statin lipid-lowering drugs in our study, could account for the somewhat smaller effect of HMG-CoA reductase inhibitors on AF risk. The beneficial impact of ACEIs/ARBs on AF observed in our study is similar to that derived from a meta-analysis of 11 studies by Healy et al.²⁰ In this analysis, the reduction in AF produced by ACEIs and ARBs was seen mostly in patients with impaired LV systolic function. Based on our data, the impact of ACEIs/ARBs on the risk of AF was more pronounced than that of β -blockers.

The LIFE (Losartan Intervention For End Point Reduction in Hypertension) study showed similar findings.²¹ Losartan produced a 33% relative reduction in the risk of new-onset AF compared with atenolol in patients with hypertension despite similar reductions in blood pressure.

To determine which subclass might be associated with the reduction in AF prevalence, we analyzed the specific lipid-lowering drug prescribed to 362 patients enrolled at Emory and Crawford Long Hospitals. In this cohort, statins were used in the majority of patients taking lipid-lowering drugs (>90% of patients were taking lipid-lowering drugs), and the combination of statins and/or fibrates was prescribed in 98% of patients taking lipid-lowering drugs. Given the ability of these drugs to modulate inflammation and oxidative

stress^{22,23} and in view of animal and preliminary human data suggesting a beneficial effect of HMG-CoA reductase inhibitors on AF, the reduction in arrhythmia prevalence observed in this study likely is mediated by these two classes of lipid-lowering drugs.^{10–13}

The proposed mechanisms by which lipid-lowering drugs reduce arrhythmias burden include reduction in coronary ischemia,²⁴ modulation of the autonomic nervous system,^{25,26} and attenuation of inflammation and reactive oxygen species production.¹¹ Based on reported data, it is plausible that inflammation, increased wall stress, and/or increased levels of angiotensin II activate Nox2-containing NAD(P)H oxidases, leading to increased production of reactive oxygen species.^{27,28} These molecules may alter channel kinetics, including inactivating the Na⁺ channel²⁹ and increasing the amplitude of the I_{Kr} current,³⁰ leading to slowing of conduction and shortening of action potential duration, promoting the initiation and perpetuation of AF. This kind of electrical remodeling may be accompanied by reactive oxygen species-mediated structural remodeling, leading to hypertrophy and fibrosis of myocytes.³¹

Statins can modulate this cascade through their anti-inflammatory and antioxidant properties. By depleting cholesterol intermediates, statins block the membrane translocation of the small G-protein rac, a necessary step in the activation of various NAD(P)H oxidases, which constitute the major sources of reactive oxygen species in the cardiovascular system.^{32–34} In addition, the anti-inflammatory role of HMG-CoA reductase inhibitors may be mediated through the activation of the PPAR_α,³⁵ in a manner similar to that of fibric acid derivatives.^{14,15}

As we observed in a prior publication using the ADVANCENTSM registry,¹⁹ age, white race, and heart failure severity were clear risk factors for the arrhythmia. However, in contrast with other reports, diabetes and coronary artery disease were associated with a reduced likelihood of AF in our study. This may be explained by the greater degree of atrial pressure and stretch seen in patients with reduced LV function and underlying hypertensive or valvular heart disease compared with those with LV systolic dysfunction of ischemic etiology. These results are further supported by data from the Cardiovascular Health Study.³⁶ Diabetes and coronary artery disease were risk factors for the development of AF in the general population but not in patients with underlying cardiovascular disease. Interestingly, the multivariable analyses showed a weakly positive association between increased LVEF and AF prevalence. This observation is a result of the inclusion of NYHA class in the statistical model. LVEF is an imperfect measure of LV function, correlating poorly with NYHA class and oxygen consumption during aerobic exercise. When NYHA class was removed from the model, this paradoxical result was no longer seen (OR for LVEF 1.002, 95% CI 0.999–1.005).

Study limitations

Our study is limited by its observational design. As a result, we could not adjust for unknown potential confounders. However, given the large population studied, the marked effect of lipid-lowering drugs on AF prevalence, and the use of multivariable regression analyses to adjust for the effects of known confounders, it is less likely that the association measured is spurious. Moreover, as a result of the cross-sectional nature of this analysis, it is difficult to ascertain the temporal relationship between lipid-lowering drug use and development of AF. However, this is more likely to blunt than to exaggerate the observed benefit of lipid-lowering drugs on arrhythmia prevalence. Given the study design, AF episodes that precede the initiation of lipid-lowering drugs are recorded as drug failure, even if the arrhythmia was successfully suppressed following the initiation of the lipid-lowering drug. We speculate that the marked beneficial effect of lipid-lowering drugs on AF risk in

this study is likely mediated by statins and fibrate drugs. Although this statement is supported by the high rate of prescription of these medications in the Emory–Crawford Long cohort, this group might not adequately represent the practice patterns of the other centers in the ADVANCENTSM registry. Despite encouraging the enrollment of consecutive patients, this voluntary registry may not be representative of the entire U.S. population with LV dysfunction secondary to the reporting bias inherent to such study designs. However, to date, ADVANCENT, with more than 25,000 patients enrolled, remains one of the larger registries of patients with heart failure. Finally, because AF was also diagnosed based on patient self-reporting, this method of data collection could introduce another reporting bias. However, the reliability of this method is supported by the significantly higher prescription of anticoagulants in the AF group, with 65% of patients taking such agents. This estimate is comparable to the rates of warfarin use in patients with electrocardiographically proven AF.^{37,38}

Conclusion

Our data suggest that lipid-lowering drug use is associated with a significant reduction in AF risk in patients with low LVEF at high risk for the arrhythmia; this reduction was the most sizeable among known prophylactic pharmacotherapies. The role of lipid-lowering drugs in the treatment of preexisting AF is not elucidated by this study and remains controversial.^{12,39}

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Figure 1.

Multivariable logistic regression analysis of atrial fibrillation (AF) risk. In multivariable regression analysis, the odds ratio for AF in patients taking lipid-lowering drugs was 0.685 (95% CI 0.636–0.737), which equals a 31.5% decrease in AF odds on such therapy. ACEI/ARB prescription had a statistically significant but more modest effect on reducing arrhythmia odds (OR 0.851, 95% CI 0.786–0.922). A trend toward reduced AF odds was noted for β -blocker but failed to reach statistical significance (OR 0.948, 95% CI 0.876–1.025). The impacts of other demographic and clinical parameters, included in the multivariable analysis, on the odds of AF are also presented. Data are presented as odds ratios, with *bars* representing the lower and upper limits of the 95% confidence interval. *The 95% CI does not cross 1. ACEI/ARB = angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CAD = coronary artery disease; HTN = hypertension; LVEF = left ventricular ejection fraction; NYHA = New York heart Association.

Figure 2.

Lipid-lowering agents reduce atrial fibrillation (AF) prevalence independent of the lipid profile. The prevalence of AF is significantly reduced in patients taking lipid-lowering agents (25.1%) vs patients with hyperlipidemia undergoing no such therapy or those without hyperlipidemia ($P < .001$ for both comparisons). The prevalence of AF was similar in the latter two groups ($P = \text{NS}$).

Table 1

Baseline characteristics of the entire cohort

Population	25,268
Age (yr)	66.4 ± 13.2
Male	18,071 (71.5%)
White race	20,836 (82.5%)
Atrial fibrillation	7,027 (27.8%)
Ischemic cardiomyopathy	18,225 (72.1%)
Left ventricular ejection fraction (%)	31.0 ± 10.5
Hypertension	18,303 (72.4%)
Hyperlipidemia	18,006 (71.3%)
Diabetes	7,914 (31.3%)
Medication	
Aspirin (acetylsalicylic acid)	15,453 (61.2%)
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	20,633 (81.7%)
β -Blocker	19,997 (79.1%)
Lipid-lowering drug	16,881 (66.8%)
Digitalis	9,084 (36.0%)
Antiarrhythmic drug	4,267 (16.9%)
Anticoagulant	7,736 (30.6%)

Data are given as number (percent) or mean ± SD.

Number of patients in subgroups may not sum to total population due to missing data.

Table 2

Impact of drugs on atrial fibrillation prevalence

Patient characteristic	Atrial fibrillation prevalence	P value
Lipid-lowering drug		<.001
Yes	4,377 (25.3%)	
No	2,650 (33.1%)	
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker		<.001
Yes	5,560 (26.7%)	
No	1,467 (32.9%)	
β -Blocker		<.001
Yes	5,460 (26.5%)	
No	1,567 (33.5%)	

Data are given as number (percent).

All data not available for all 7,027 patients with atrial fibrillation.

Table 3

Covariate-adjusted medication effect on the odds of atrial fibrillation

	Odds ratio	95% Confidence interval
Lipid-lowering drug	0.68	0.64–0.74
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker	0.85	0.79–0.92
β -Blocker	0.95	0.88–1.02
Antiarrhythmic drug	4.13	3.84–4.45