Atrial Fibrillation in Hypertension
Predictors and Outcome

Paolo Verdecchia, GianPaolo Reboldi, Roberto Gattobigio, Maurizio Bentivoglio, Claudia Borgiaoni, Fabio Angeli, Erberto Carluccio, Maria Grazia Sardone, Carlo Porcellati

Abstract—Incidence, determinants, and outcome of atrial fibrillation in hypertensive subjects are incompletely known. We followed for up to 16 years 2482 initially untreated subjects with essential hypertension. At entry, all subjects were in sinus rhythm. Subjects with valvular heart disease, coronary artery disease, preexcitation syndrome, thyroid disorders, or lung disease were excluded. During follow-up, a first episode of atrial fibrillation occurred in 61 subjects at a rate of 0.46 per 100 person-years. At entry, subjects with future atrial fibrillation differed (all P<0.05) from those without by age (59 versus 51 years), office, and 24-hour systolic blood pressure (165 and 144 versus 157 and 137 mm Hg, respectively), left ventricular mass (58 versus 49 g/height[m]2.7), and left atrial diameter (3.89 versus 3.56 cm). Age and left ventricular mass (both P<0.001) were the sole independent predictors of atrial fibrillation. For every 1 standard deviation increase in left ventricular mass, the risk of atrial fibrillation was increased 1.20 times (95% CI, 1.07 to 1.34). Atrial fibrillation became chronic in 33% of subjects. Age, left ventricular mass, and left atrial diameter (all P<0.01) were independent predictors of chronic atrial fibrillation. Ischemic stroke occurred at a rate of 2.7% and 4.6% per year, respectively, among subjects with paroxysmal and chronic atrial fibrillation. These data indicate that in hypertensive subjects with sinus rhythm and no other major predisposing conditions, risk of atrial fibrillation increases with age and left ventricular mass. Increased left atrial size predisposes to chronicization of atrial fibrillation. (Hypertension. 2003; 41:218-223.)

Key Words: fibrillation ■ hypertension, essential ■ stroke ■ hypertrophy ■ echocardiography ■ aging

The most important risk factors for atrial fibrillation (AF) are age, male gender, hypertension, thyrotoxicosis, smoking, diabetes, left ventricular (LV) hypertrophy, left atrial enlargement, valvular and coronary heart disease, congestive heart failure, and stroke.1–5 In the Framingham Heart Study, hypertension and diabetes were the sole cardiovascular risk factors to be predictive of AF after controlling for age and other predisposing conditions.5

The role of hypertension as risk factor for AF is established but still incompletely known. In the Manitoba Follow-up study, prevalence of hypertension was 53%, and the risk of AF was 1.42 times higher in hypertensive subjects as compared with normotensive subjects.2 Because of its high prevalence in the population, hypertension independently accounts for more AF cases than any other risk factor.5 However, despite its leading importance as a highly prevalent and modifiable risk factor, only a few data are available regarding predictors and outcome of AF in large populations of subjects with essential hypertension free of coexisting valvular or coronary heart disease, congestive heart failure, hyperthyroidism, or other predisposing conditions. In particular, the clinical value of LV mass as a potential independent predictor of AF in the specific setting of essential hypertension has never been examined in a large cohort of subjects.

Methods
The Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study started in 1986 as an observational registry of morbidity and mortality in initially untreated subjects with essential hypertension. Details on protocol have been published previously.6–8 The protocol was approved by the local ethics committee. Briefly, all subjects had an average of at least 3 measurements of office blood pressure (BP) ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic on at least 3 visits. Ambulatory BP was recorded with an oscillometric device (SpaceLabs), set to take a reading every 15 minutes throughout 24 hours. Standard 12-lead ECG was recorded at 25 mm/s (1-mV/cm calibration). None of the subjects was receiving digitalis. The Perugia index, previously developed and validated in our laboratory,9,10 was used for ECG diagnosis of LV hypertrophy. The index requires positivity of at least 1 of the following: SV1 + RaVL ≥2.4 mV (men) or ≥2.0 mV (women), typical LV strain, or a Romhilt-Estes score of ≥5.10

The M-mode echocardiographic study of the LV was performed under 2-dimensional control. Details about reading procedures and reproducibility in our laboratory are reported elsewhere.7 LV mass was calculated according to Devereux11 and corrected by height in meters at the power of 2.7 to correct for overweight and obesity.12 LV hypertrophy was defined by a LV mass >49.2 g/m2.7 in men and
Relative wall thickness was calculated as [(posterior wall thickness/2)/LV internal diameter]. According to de Simone and coworkers, LV mechanics were assessed at midwall level according to a geometric model that takes into account the nonuniform systolic thickening of the LV wall. Pulsed Doppler measurements of LV diastolic inflow were obtained as reported previously. The LV diastolic filling pattern was recorded from the apical position on subjects in partial left lateral decubitus during expiratory apnea, with the sample volume between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and the peak velocity of atrial filling (A velocity) were recorded and the A-to-E ratio (A/E) was calculated. Tracings were read by 2 observers who were unaware of patients’ clinical data, and the mean value from ≥5 measurements per observer was computed.

All subjects were in sinus rhythm, and none had valvular heart disease, coronary artery disease, preexcitation syndrome, thyroid disorders, or lung disease.

Follow-Up
Follow-up was mostly in charge of family doctors, in cooperation with our hospital staff. Antihypertensive treatment was aimed at reducing office BP to <140/90 mm Hg, by means of lifestyle and pharmacological measures. Diuretics, β-blockers, ACE inhibitors, calcium channel blockers, and α-blockers, alone or combined, were the antihypertensive drugs most frequently used.

Assessment of End Points
Periodical contacts with family doctors and phone interviews with patients were arranged to ascertain occurrence of new cases of AF. AF was assessed on the surface ECG by absence of P waves before each QRS complex, irregular atrial electrical activity with f waves varying in size, shape and timing, and irregular ventricular rate. Only cases of AF documented by available ECG tracings were considered for this study. Paroxysmal AF was defined by a single or multiple occurrence of AF that resolved during hospitalization, either spontaneously or for effect of treatment. Subjects in whom sinus rhythm could not be maintained despite multiple pharmacological or electric attempts of cardioversion were coded as chronic AF. Hyperthyroidism was assessed and ruled out in all subjects with incident AF. Stroke was defined as a new neurological deficit lasting >24 hours in the absence of underlying potentially important nonvascular causes. Patients with stroke were hospitalized during the acute phase, and brain imaging and other diagnostic tests were carried out to exclude cerebral hemorrhage.

Statistical Analysis
Statistical analysis was performed with SPSS (SPSS Inc) and SAS-Stat (SAS Institute). Parametric data are reported as mean±SD. For subjects who had multiple paroxysmal episodes of AF, trial time to event was defined as that to the first episode. Survival curves were estimated by means of the Kaplan-Meier product-limit method and compared by means of the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated with stepwise Cox models. We tested the following covariates: age (years), gender (women, men), family history of premature cardiovascular disease (no, yes), diabetes (no, yes), serum cholesterol (mmol/L), smoking habits (nonsmokers, current smokers), body mass index (kg/m²), office systolic and diastolic BP (mm Hg), average 24-hour systolic and diastolic BP (mm Hg), LV hypertrophy at ECG (yes, no), LV mass (kg/height¹⁵), left atrial diameter (cm), negative P-wave component exceeding 0.1 mV×0.04 seconds in lead V₁ (yes, no), peak-A velocity, peak-E velocity and their ratio, antihypertensive treatment at follow-up (lifestyle measures alone, diuretics and β-blockers alone or combined, ACE inhibitors and calcium antagonists alone or combined, other drug combinations). All univariate and multivariate analyses that included echocardiographic variables were automatically restricted to the subset with available echocardiographic tracings (n=2075).

In 2-tailed tests, probability values <0.05 were considered statistically significant.

Results
Characteristics of the Population
We obtained complete follow-up data from 2482 (98.1%) of the 2529 subjects who entered the study. The mean baseline characteristics of the population are shown in Table 1. The mean duration of follow-up was 5.3 years (range, 1 to 16), for a total of 13 161 patient-years of observation. At entry, subjects with future AF were older and had an increased body mass index, a higher office and ambulatory systolic BP, and a lower heart rate when compared with those without future AF. The greater LV mass in the subset with future AF was accounted for by a greater thickness of septum and posterior wall. LV internal diameter did not differ between the 2 groups. Left atrial diameter and the peak A/peak E ratio were increased in the subset with future AF. A final negative component of the P wave in lead V₁ ≥0.04 seconds×0.1 mV was more frequent among subjects with future AF than in the other group.

At entry, prevalence of LV hypertrophy at ECG was 17.1% in the total population, 25.5% among subjects in whom AF subsequently developed, and 16.9% among those in whom AF did not develop (P<0.01).

Echocardiograms were not obtained because of administrative reasons in 110 subjects. In the remaining 2372, echocardiographic tracings were of good quality for determination of LV mass in 2075 subjects (87.5%). Subjects with available echocardiographic tracings were younger (50 versus 58 years, respectively; P<0.001) and less frequently diabetic (5.4% versus 16%) than those without available tracings. Body mass index was less in the subset with than in that without echocardiographic tracings (26.6 versus 27.7 g/m²; P=0.001). Office systolic BP (157 versus 160 mm Hg, P<0.001) but not 24-hour ambulatory BP (137 versus 137 mm Hg; P=NS) was lower in the group with available echocardiographic tracings. Diastolic BP, both office (97 versus 96 mm Hg; P=0.014) and 24-hour ambulatory (87 versus 85 mm Hg; P<0.001), was higher in the subset with available echocardiographic tracings than in the other group.

Prevalence of LV hypertrophy at echocardiography was 47.8% in the total population and significantly more frequent (P<0.01) in the subset with future AF (68.0%) than in that without AF (47.3%).

Predictors of Atrial Fibrillation
AF occurred in 61 subjects at a rate of 0.46% per year. Twenty-eight of these subjects had an isolated episode of AF; 13 had recurrent AF, and 20 had chronic AF. The rate of chronic AF was 0.15% per year. Age and LV mass (Table 2) were the sole independent predictors of AF. After adjustment for age, left atrial diameter predicted AF (P=0.005), but its significance was lost after correction for LV mass. There was a significant association between LV mass and left atrial diameter, either unadjusted (r=0.34; P=0.0001) or corrected for body surface area (r=0.24; P=0.0001). ECG signs of left atrial enlargement (negative component of the P wave in V₁≥0.1 mV×0.08 seconds) were associated with a 2-fold increased risk of AF (relative risk, 2.17; 95% CI, 1.18 to 4.01) after adjustment for age, but their significance was lost after
controlling for LV mass. Office and ambulatory BP, LV hypertrophy at ECG, and the peak A/peak E ratio on transmitral Doppler flow were neither univariate nor multivariate predictors of AF. Neither the Cornell voltage (sum of R wave in aVL plus S wave in V3) nor the Sokolow-Lyon voltage (S wave in V1 plus the tallest R wave in V5 or V6) were predictors of the risk of AF (all \(P/N.S.)

For every 14 g/height\(^{2.7}\) increase in LV mass, the independent risk of AF increased by 1.73 times (95% CI, 1.34 to 2.24). The risk of AF increased by 1.45 times (95% CI, 1.16 to 1.83) for every 0.094 (1 SD) increase in relative wall thickness (\(P/0.001\)), but its significance was lost after correction for LV mass. Furthermore, the risk of AF decreased (relative risk, 0.66; 95% CI, 0.50 to 0.88) for every 3.22% (1 SD) increase in midwall shortening fraction (\(P/0.004\)), but its significance was lost after adjustment for LV mass.

Figure 1 shows the cumulative incidence and the crude rate of chronic AF at different levels of LV mass and left atrial diameter.

Stroke occurred in 107 of the 2421 subjects without AF at a rate of 0.81% per year, in 5 of the 41 subjects with paroxysmal AF at a rate of 2.7% per year, and in 6 of the 20 subjects with chronic AF at a rate of 4.6% per year (log-rank test: \(P/0.0005\)). Stroke rate in the overall group of patients

### TABLE 1. Baseline Characteristics of Patients With and Without Future Occurrence of Atrial Fibrillation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Population (N=2482)</th>
<th>Future Occurrence of Atrial Fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n=2421)</td>
<td>Yes (n=61)</td>
</tr>
<tr>
<td>Age, y</td>
<td>51 (12)</td>
<td>59 (10)*</td>
</tr>
<tr>
<td>Gender, % men</td>
<td>53.2</td>
<td>52.5</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>26.8 (4)</td>
<td>28.0 (4)*†</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>7.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>22.8</td>
<td>23.0</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg</td>
<td>157 (19)</td>
<td>165 (21)*</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg</td>
<td>97 (10)</td>
<td>95 (12)</td>
</tr>
<tr>
<td>Office HR, beats/min</td>
<td>75 (10)</td>
<td>72 (9)*†</td>
</tr>
<tr>
<td>24-hour systolic BP, mm Hg</td>
<td>137 (15)</td>
<td>144 (15)*</td>
</tr>
<tr>
<td>24-hour diastolic BP, mm Hg</td>
<td>87 (10)</td>
<td>88 (11)</td>
</tr>
<tr>
<td>24-hour HR, beats/min</td>
<td>75 (9)</td>
<td>72 (10)†</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.6 (1.3)</td>
<td>5.9 (1.9)</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>87.1 (21.8)</td>
<td>90.3 (25)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.6 (1.1)</td>
<td>5.5 (1.1)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.3 (0.3)</td>
<td>1.2 (0.3)</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>3.6 (0.9)</td>
<td>3.4 (1.0)</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.6 (1.1)</td>
<td>1.9 (1.4)</td>
</tr>
<tr>
<td>Potassium, mmol/L</td>
<td>4.2 (0.4)</td>
<td>4.1 (0.4)</td>
</tr>
<tr>
<td>LV hypertrophy at ECG, %</td>
<td>17.1</td>
<td>25.5*</td>
</tr>
<tr>
<td>Interventricular septum, cm</td>
<td>1.12 (0.23)</td>
<td>1.26 (0.28)*†</td>
</tr>
<tr>
<td>LV internal diameter, cm</td>
<td>4.95 (0.52)</td>
<td>5.04 (0.63)</td>
</tr>
<tr>
<td>LV posterior wall, cm</td>
<td>1.00 (0.18)</td>
<td>1.08 (0.20)*†</td>
</tr>
<tr>
<td>LV mass, g/height(^{2.7})</td>
<td>49 (14)</td>
<td>58 (20)*†</td>
</tr>
<tr>
<td>Relative wall thickness</td>
<td>0.43 (0.09)</td>
<td>0.47 (0.11)*†</td>
</tr>
<tr>
<td>Midwall shortening fraction, %</td>
<td>16.6 (3.2)</td>
<td>15.5 (3.4)*†</td>
</tr>
<tr>
<td>Left atrial diameter, cm</td>
<td>3.75 (0.7)</td>
<td>3.89 (0.7)*†</td>
</tr>
<tr>
<td>Peak A/Peak E ratio</td>
<td>1.10 (0.43)</td>
<td>1.20 (0.41)*†</td>
</tr>
<tr>
<td>Negative P wave component in V(_1)&gt;0.04 sec×0.1 mV, %</td>
<td>15.7</td>
<td>25.5†</td>
</tr>
<tr>
<td>LV hypertrophy at echocardiography, %</td>
<td>47.8</td>
<td>68.0*</td>
</tr>
</tbody>
</table>

Data are expressed as mean (±SD). BP indicates blood pressure; HR, heart rate; HDL, high density lipoprotein; LDL, low density lipoprotein; LV, left ventricular; and ECG, electrocardiography.

*\(P<0.01\), †\(P<0.05\) vs subjects without atrial fibrillation. The echocardiographic results refer to the 2075 subjects with good-quality echocardiographic tracings.
with incident AF was 2.46% per year (P<0.0001 versus subjects without AF). Anticoagulant therapy with warfarin was taken by none of the subjects without AF, 2 of the subjects with paroxysmal AF, and 6 of the subjects with chronic AF. None of the subjects treated with warfarin had a stroke.

**Discussion**

This study is the first to examine incidence, determinants, and outcome of AF in a large cohort of initially untreated subjects with essential hypertension, sinus rhythm, and absence of valvular heart disease, coronary artery disease, preexcitation syndrome, thyroid disorders, or lung disease. Subjects were included independent of their LV mass and atrial diameter to evaluate the impact of these parameters, as specifically related to the hypertensive state, on the risk of subsequent AF.

**Previous Studies**

In general population studies, hypertension was an independent risk factor for AF. The risk of AF in hypertensive compared with normotensive subjects was increased by 1.9 times in the Framingham Heart Study and 1.4 times in the Manitoba Follow-up Study. However, the independent impact of hypertension on AF was estimated through statistical control of several confounders including valvular heart disease, coronary artery disease, preexcitation syndrome, thyroid disorders, or lung disease. Subjects were included independent of their LV mass and atrial diameter to evaluate the impact of these parameters, as specifically related to the hypertensive state, on the risk of subsequent AF.

Since hypertension may be found frequently in the above clinical conditions, extrapolations of results to uncomplicated hypertensive subjects with possible coexistence of LV hypertrophy as specifically related to hypertensive state may be difficult. For example, the Framingham Heart Study showed that the age-adjusted risk of AF associated with hypertension decreased from 1.8 to 1.5 in men and from 1.7 to 1.4 in women after controlling for other associated conditions.

Therefore, identification of hypertensive subjects more likely to have AF in the future is made difficult by the paucity of epidemiological data. Ciaroni and coworkers examined 97 initially untreated hypertensive subjects, 19 in whom AF developed over a follow-up period of 25 months. In addition to age and LV mass, other independent predictors of AF were daytime and nighttime ambulatory systolic BP, maximal duration and dispersion of the P waves, left atrial dimension, and the peak velocity of the A wave. In our study, carried out in a larger population, office BP, ambulatory BP, and the Doppler indexes of transmitral flow were not predictive of AF. On the other hand, the ECG signs of left atrial enlargement and left atrial size at echocardiography were predictors of AF, but their significance was lost after correction for LV mass. Left atrial diameter remained an independent predictor of chronic AF even after adjustment for age and LV mass. The larger sample size, longer observation time, and more numerous AF events strengthen our results. Part of differences between the 2 studies could be related to different clinical features of subjects at entry. In our study, subjects were younger (51 years) and their office BP (157/97 mm Hg)
LV mass is strongly predictive of cardiovascular complications in the general population and in a variety of clinical conditions, including essential hypertension. It is generally believed that LV mass reflects and integrates the cumulative long-term effects of several hemodynamic and nonhemodynamic factors that may exert detrimental effects on cardiovascular system. In the Cardiovascular Health Study, LV mass was not an independent predictor of AF, but echocardiographic data were missing in about one third of subjects. In the Framingham study, the sum of septal and posterior wall thickness was an independent predictor of AF, but results of multivariate analysis with regard to LV mass were not reported. Thus, our study is the first to substantiate the role of LV mass as an independent predictor of AF in apparently uncomplicated subjects with essential hypertension.

Left atrial dilation was a precursor of AF in the Framingham Heart Study and the Cardiovascular Health Study. Electrophysiological features associated with left atrial dilation include shortening of the refractory period and prolongation of conduction time. Both these alterations may lead to development of multiple reentrant wave fronts starting and possibly perpetuating AF. Our findings suggest that left atrial dilation in hypertensive subjects who are in sinus rhythm is valuable to identify those individuals more prone to have chronicization of AF. Since atrial diameter was measured by M-mode echocardiography in the parasternal approach and anteroposterior section, the use of 2-dimensional echocardiography and multiple planes for measurements might lead to different predictive results.

The E- and A-wave velocities on the transmitral inflow pattern, as well as their ratio, did not predict occurrence of AF. In the study by Ciaroni and coworkers, only the A-wave velocity was a predictor of AF. In a study by Mattioli and coworkers, patients with recurrence of AF were more likely to have a larger left atrium and a smaller A-wave after cardioversion. The possibility that LV diastolic dysfunction may contribute to trigger AF in uncomplicated hypertensive subjects through an increase in left atrial pressure is attractive but difficult to investigate in epidemiological studies. For example, it is well known that the transmitral Doppler flow velocity pattern may be influenced by several conditions unrelated to diastolic dysfunction that include age, heart rate, and LV filling pressure.

Ischemic Stroke
Among subjects with AF, hypertension portends an increased risk of stroke. Crude stroke rate in our population was 2.7% per year among subjects with paroxysmal AF and 4.6% per year among those with chronic AF. Only 2 subjects with paroxysmal AF and 6 subjects with chronic AF received treatment with warfarin, and none of them had a stroke. The surprisingly low use of warfarin in these subjects might be explained by the perception by family doctors of an unfavorable risk-benefit ratio associated with anticoagulation in hypertensive subjects not complicated by heart failure or valvular disease. By contrast, the high incidence of stroke in the present study supports the use of warfarin in apparently uncomplicated hypertensive subjects who have AF.

Limitations
Some limitations must be acknowledged. First, since the PIUMA population is composed of white subjects, caution is needed when results are extrapolated to different ethnic groups. Second, similar to most observational cohort studies, we were unable to control for occasional changes in treatment over time. Third, we could not assess the impact of serial changes in BP and LV mass on the subsequent risk of AF in a sufficiently large number of subjects. Indeed, no more than 40% of the entire population repeated a complete clinical visit and an echocardiography study of the LV during follow-up before incident AF. Finally, 3 independent predictors of chronic atrial fibrillation were selected in a model with 20 outcome events (Table 2). It is generally believed that 10 outcome events are needed for every independent predictor selected by a model to minimize risk of statistical overfitting.

Conclusions
In untreated hypertensive subjects in sinus rhythm and free of overt cardiovascular disease or hyperthyroidism, age and LV mass are the sole independent predictors of AF. Left atrial size is a further independent predictor of chronicization of AF. The high rate of ischemic stroke in our population supports a larger use of warfarin in apparently uncomplicated hypertensive subjects with incident AF.

Perspectives
The present study was undertaken to detect predictors and outcome of atrial fibrillation in a large cohort (n=2482) of hypertensive subjects who contributed 13 161 patient-years of observation and 61 cases with new-onset atrial fibrillation. Occurrence of atrial fibrillation was independently predicted by age and LV mass at echocardiography, whereas left atrial diameter was an independent predictor of chronicization of atrial fibrillation. Only 30% of subjects whose atrial fibrillation became chronic and 4.9% of subjects with paroxysmal atrial fibrillation received treatment with warfarin by their family doctors. An ischemic stroke occurred in 12.1% of subjects with paroxysmal atrial fibrillation detected by echocardiography for prediction of atrial fibrillation and its chronicization in hypertensive subjects who are in sinus rhythm. Furthermore, these data suggest a more liberal use of warfarin for prevention of stroke in hypertensive subjects with chronic and perhaps paroxysmal AF.

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References


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