

Pulse Pressure and Risk of New-Onset Atrial Fibrillation

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ATRIAL FIBRILLATION (AF) IS the most common chronic arrhythmia in adults and is associated with increased risk for mortality and stroke.¹⁻³ An estimated 2.3 million adults in the United States have AF currently, and that number is expected to increase substantially as the population ages.^{4,5} The prevalence of AF increases markedly with age,⁴ with a substantial overall lifetime risk of approximately 1 in 4 for both men and women.⁶ Investigators have identified several key clinical risk factors for AF including advancing age, increased systolic blood pressure, diabetes, hypertension, heart failure, valvular disease, myocardial infarction, and obesity.⁷⁻⁹ Echocardiographic risk factors for nonrheumatic AF include left atrial enlargement, increased left ventricular wall thickness, and impaired left ventricular systolic function.^{8,10}

The exponential rise in AF incidence with age parallels a rapid age-related increase in aortic stiffness. The concomitant increase in pulse pressure adds to pulsatile load on the heart,¹¹ thereby promoting ventricular hypertrophy,¹² impaired ventricular relaxation,¹³⁻¹⁵ and increased left atrial size.¹⁶ Elevated left atrial

Context Atrial fibrillation (AF) is responsible for considerable morbidity and mortality, making identification of modifiable risk factors a priority. Increased pulse pressure, a reflection of aortic stiffness, increases cardiac load and may increase AF risk.

Objective To examine relations between pulse pressure and incident AF.

Design, Setting, and Participants Prospective, community-based observational cohort in Framingham, Mass, including 5331 Framingham Heart Study participants aged 35 years and older and initially free from AF (median age, 57 years; 55% women).

Main Outcome Measures Incident AF.

Results AF developed in 698 participants (13.1%) a median of 12 years after pulse pressure assessment. Cumulative 20-year AF incidence rates were 5.6% for pulse pressure of 40 mm Hg or less (25th percentile) and 23.3% for pulse pressure greater than 61 mm Hg (75th percentile). In models adjusted for age, sex, baseline and time-dependent change in mean arterial pressure, and clinical risk factors for AF (body mass index, smoking, valvular disease, diabetes, electrocardiographic left ventricular hypertrophy, hypertension treatment, and prevalent myocardial infarction or heart failure), pulse pressure was associated with increased risk for AF (adjusted hazard ratio [HR], 1.26 per 20-mm Hg increment; 95% confidence interval [CI], 1.12-1.43; $P < .001$). In contrast, mean arterial pressure was unrelated to incident AF (adjusted HR, 0.96 per 10-mm Hg increment; 95% CI, 0.88-1.05; $P = .39$). Systolic pressure was related to AF (HR, 1.14 per 20-mm Hg increment; 95% CI, 1.04-1.25; $P = .006$); however, if diastolic pressure was added, model fit improved and the diastolic relation was inverse (adjusted HR, 0.87 per 10-mm Hg increment; 95% CI, 0.78-0.96; $P = .01$), consistent with a pulse pressure effect. Among patients with interpretable echocardiographic images, the association between pulse pressure and AF persisted in models that adjusted for baseline left atrial dimension, left ventricular mass, and left ventricular fractional shortening (adjusted HR, 1.23; 95% CI, 1.09-1.39; $P = .001$).

Conclusion Pulse pressure is an important risk factor for incident AF in a community-based sample. Further research is needed to determine whether interventions that reduce pulse pressure will limit the growing incidence of AF.

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size and pressure and impaired ventricular diastolic function may lead to fibrosis and electrical remodeling in the atrium, providing a substrate for the development of AF. Consistent with this causal pathway, echocardiographic measures of abnormal left ventricular diastolic function are associated with increased risk for developing AF.^{17,18}

Thus, age-associated increased pulsatile load (as measured with pulse pressure) may be a key determinant of the increasing incidence of AF in the el-

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derly. Prior studies have shown that systolic pressure is related to subsequent risk for development of AF.⁸ Yet, to our knowledge, the relative contribution of mean and pulsatile blood pressure components to the risk of developing AF has not been evaluated comprehensively. Accordingly, we tested prospectively the hypothesis that pulse pressure may represent an easily measured and potentially modifiable risk factor for the development of AF in the large community-based Framingham Study sample.

METHODS

Study Sample

The design and selection criteria of the Framingham Heart Study and the Framingham Offspring Study have been detailed previously.^{19,20} Participants attending the 16th examination of the original cohort (n=2351; 1979-1982) or the second examination of the offspring cohort (n=3863; 1979-1983) were eligible for the present investigation. These evaluations are referred to as the baseline examination for the present investigation. We excluded participants for the following reasons: age younger than 35 years (n=701); prior or current AF (n=127); or missing covariate or follow-up information (n=55), resulting in a sample of 5331 participants (2202 original cohort participants [41%]; 2946 women [55%]). All protocols were approved by the Boston University Medical Center institutional review board and participants provided written informed consent.

Clinical Evaluation and Definitions

Medical history, physical examination, and electrocardiography were routinely administered at each Framingham Heart Study examination.^{19,20} Blood pressure represented the average of 2 seated auscultatory blood pressure readings obtained by the physician at the time of each Framingham clinic examination. Pulse pressure was calculated as the difference between systolic and diastolic pressure. Mean arterial pressure was calculated as dia-

stolic pressure plus one third of pulse pressure.

Height and weight were measured directly using a standardized protocol. Body mass index was calculated by dividing weight in kilograms by the square of the height in meters. Criteria for diabetes mellitus were a fasting glucose level of 126 mg/dL (7.0 mmol/L) or greater, random glucose level of 200 mg/dL (11.1 mmol/L) or greater, or use of insulin or medications used to treat hyperglycemia. Electrocardiographic left ventricular hypertrophy was defined as increased voltage with accompanying lateral repolarization abnormalities.²¹

A standardized 2-dimensional guided M-mode echocardiogram also was performed at the baseline examinations.²² Left atrial diameter at end-systole was measured according to American Society of Echocardiography guidelines.²³

Medical records were obtained for all hospitalizations and follow-up physician visits related to cardiovascular disease and were reviewed by a committee of 3 investigators; events were adjudicated following written guidelines. Criteria for other cardiovascular events, including myocardial infarction and heart failure, have been described previously.²⁴

Atrial Fibrillation

Participants were diagnosed with AF if AF or atrial flutter was present on an electrocardiogram obtained from a hospital or physician chart or from a routine Framingham clinic examination (every 2 years in the original cohort and every 4-8 years in the offspring cohort). The electrocardiographic interpretation of AF was confirmed by 1 of 2 Framingham Heart Study cardiologists (D.L. or E.J.B.).

Statistical Analyses

First, we examined the association between pulse pressure and the risk of developing new-onset AF using Cox proportional hazards regressions.²⁵ We tested for an interaction between follow-up time and pulse pressure to de-

termine whether the assumption of proportional hazards for prediction of AF was valid. Death was treated as a censoring event. Follow-up also was censored after 20 years, with the final participant censored in this manner in December 2004. Estimates were adjusted to account for competing risk from mortality during the follow-up period.²⁶ Covariates selected for adjustment were based on prior reports^{7,9} and included the following at the baseline examination: age, sex, body mass index, regular use of cigarettes in the prior year, use of antihypertensive therapy, diabetes mellitus, electrocardiographic (ECG) left ventricular hypertrophy, history of myocardial infarction or heart failure, and valvular disease (defined as significant systolic murmur, grade 3 or greater out of 6, or any diastolic murmur identified at the Framingham clinic examination). In additional models, we examined whether pulse pressure predisposed to AF through an interim change in pulse pressure or any of the other clinical risk factors (considered as time-dependent covariates).

Second, we investigated relations between AF and the various components of blood pressure (systolic, diastolic, mean, and pulse pressure). Effect sizes in these models were per 20 mm Hg for systolic and pulse pressure and 10 mm Hg for diastolic and mean pressure, which is equivalent to approximately 1 SD for each variable. We assessed the significance of adding variables to blood pressure models using χ^2 tests based on changes in log likelihood.

Third, we explored whether the relation between pulse pressure and AF may be mediated by the influence of pulse pressure on left atrial or ventricular structure and function.^{16,27} To examine this, we constructed a multivariable model with adjustment for echocardiographic left atrial size, left ventricular mass, and fractional shortening measured at the baseline examination. Values for left atrial size, left ventricular mass, and fractional shortening were imputed if missing by using

linear regression on height and covariates from prior hazards models. Left atrial size had the least missing data so it was imputed first, left ventricular mass was imputed accounting for left atrial size (observed or imputed), and fractional shortening was imputed accounting for left atrial size and left ventricular mass (observed or imputed). A Cox model for onset of AF was refitted with these additional echocardiographic variables.

For descriptive purposes, we generated adjusted cumulative incidence curves from estimated hazard functions for AF and for survival (free of AF; free of mortality) in separate proportional hazards models. Estimates were made at age 57 years for men and women separately and for each pulse pressure group. Components were recombined to estimate cumulative incidence for each sex within each pulse pressure group and cumulative incidence curves were averaged across sexes using the proportional distribution in the overall sample.

We tested for effect modification of pulse pressure with age (older or younger than median), sex, and obesity (body mass index above or below 30) by including interaction terms for these variables and pulse pressure in separate models that also adjusted for known risk factors for AF.

All analyses were performed using SAS version 8.1.²⁸ A 2-sided *P* value < .05 was considered statistically significant.

RESULTS

Study Sample

Baseline characteristics of the study sample grouped according to approximate quartiles of pulse pressure at the time of the initial examination are presented in TABLE 1. Mean age was 56 (range, 35-90) years in men and 58 (35-91) years in women. Mean pulse pressure was 51 (SD, 15) mm Hg in men and 53 (SD, 18) mm Hg in women. Pulse pressure correlated highly with systolic pressure (calculated using Pearson correlation coefficient [*r*]=0.87; *P*<.001), moderately with mean arterial pressure (*r*=0.53; *P*<.001), and

Table 1. Baseline Characteristics of the Sample*

Variable	Quartiles of Pulse Pressure, mm Hg			
	≤40	41-49	50-61	>61
No. of patients	1339	1358	1341	1293
Women, No. (%)	750 (56.0)	679 (50.0)	733 (54.7)	784 (60.6)
Age, y	47 (10)	52 (12)	60 (12)	69 (10)
Systolic pressure, mm Hg	112 (10)	123 (10)	135 (10)	155 (17)
Diastolic pressure, mm Hg	77 (9)	78 (9)	80 (10)	79 (11)
Mean arterial pressure, mm Hg	88 (9)	93 (9)	98 (10)	104 (12)
Body mass index†	25.3 (4.0)	25.9 (4.2)	26.6 (4.7)	26.8 (4.6)
Valvular disease, No. (%)	10 (0.8)	12 (0.9)	37 (2.8)	84 (6.5)
Prior myocardial infarction, No. (%)	30 (2.2)	34 (2.5)	47 (3.5)	72 (5.6)
History of heart failure, No. (%)	4 (0.3)	2 (0.2)	14 (1.0)	28 (2.2)
Antihypertensive medication, No. (%)	114 (8.5)	217 (16.0)	359 (26.8)	513 (39.7)
Diabetes, No. (%)	34 (2.5)	68 (5.0)	96 (7.2)	171 (13.2)
Left ventricular hypertrophy by electrocardiography, No. (%)	4 (0.3)	9 (0.7)	15 (1.1)	36 (2.8)
Current smoker, No. (%)	465 (34.7)	444 (32.7)	372 (27.7)	282 (21.8)
Incident atrial fibrillation, No. (%)	75 (5.6)	123 (9.1)	199 (14.8)	301 (23.3)

*Values are mean (SD) except as noted.

†Calculated as weight in kilograms divided by height in meters squared.

weakly with diastolic pressure (*r*=0.07; *P*<.001). Systolic pressure correlated moderately with diastolic pressure (*r*=0.55; *P*<.001).

Incidence of Atrial Fibrillation

During a mean of 16 years of follow-up (censored at 20 years), 363 men and 335 women developed AF with a median time-to-event of 12 years. The unadjusted cumulative 20-year incidence of AF increased steeply across pulse pressure groups (Table 1). Prior to developing AF, 62 men and 33 women experienced a myocardial infarction and 46 men and 41 women had experienced heart failure. During the follow-up period, 1956 participants (994 women) died, of whom 1523 (778 women) were free of AF. There was no interaction between follow-up time and pulse pressure for prediction of AF in the primary Cox model, suggesting that the proportional hazards assumption was appropriate.

The FIGURE displays estimated cumulative incidences of AF (adjusted for sex and baseline age, and accounting for competing risk of mortality), and shows that the probability of developing AF over time increased with increasing pulse pressure.

Multivariable Analyses of Clinical Models

Results of Cox proportional hazards models relating pulse pressure to the incidence of AF are shown in TABLE 2. In model 1, adjusting for age and sex, a 20 mm Hg increase in pulse pressure was associated with a 34% increase in the risk for developing AF (95% confidence interval [CI], 22%-47%; *P*<.001). The association between pulse pressure and AF remained significant (*P*<.001) in model 2, which further adjusted for mean arterial pressure and clinical risk factors for AF; each 20 mm Hg increase in pulse pressure was associated with a 24% increase (95% CI, 11%-39%; *P*<.001) in the risk for developing AF. In contrast, mean arterial pressure was not associated with increased risk for developing AF in model 2 (Table 2). Since elevated pulse pressure may affect other covariates in the model, which then predispose to development of AF, we incorporated all variables in model 2 as time-dependent covariates with essentially unaltered results (model 3, Table 2).

In TABLE 3 we display the relative contribution of individual blood pressure components and their change over time to risk for AF in the Cox model

adjusted for clinical covariates (model 3, Table 2). If single blood pressure components were assessed, the associations between either systolic pressure or pulse pressure and AF were highly significant, whereas the associations between mean arterial pressure or diastolic pressure and AF were not significant (Table 3). If diastolic pressure was added to the systolic pressure model, the change (-2 log likelihood) was significant ($\chi^2=6.74$; $P=.01$;

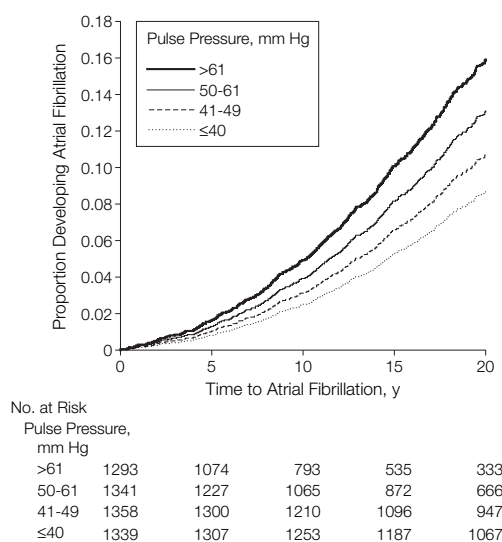
Table 3). Both blood pressure components were related to risk for AF in this dual component model and the effects were opposite in direction, indicating that for a given systolic pressure, lower diastolic pressure (and hence, higher pulse pressure) was associated with higher risk for developing AF. In contrast, if diastolic pressure was added to the pulse pressure model, the change (-2 log likelihood) was not significant ($\chi^2=0.76$; $P=.38$) and the hazard ratio

(HR) for diastolic pressure did not differ significantly from 1 (Table 3).

Multivariable Analyses of Echocardiographic Models

We hypothesized that the observed relation between pulse pressure and risk for developing AF may be attributable in part to the effects of abnormal arterial stiffness on pulsatile load and left ventricular structure and function, leading to abnormal left atrial structure and function. To test this hypothesis, we next added baseline echocardiographic left ventricular fractional shortening, left ventricular mass, and left atrial diameter to model 3 of Table 2, which included time-dependent clinical variables, pulse pressure, and mean arterial pressure. Left ventricular fractional shortening and left ventricular mass were significantly related to incident AF in these models. Pulse pressure remained a significant predictor in this model (HR, 1.23; 95% CI, 1.09-1.39; $P=.001$). In a secondary analysis, we excluded people with imputed echocardiographic data, which reduced the number of AF events from 698 to 464. The pulse pressure effect was comparable in this model, although the P value was borderline because of reduced power (HR, 1.17; 95% CI, 1.00-1.38; $P=.05$).

Figure. Incidence of Atrial Fibrillation According to Quartiles of Pulse Pressure



Estimates of cumulative incidence of atrial fibrillation according to quartile of pulse pressure. Cut points denoting approximate quartiles of pulse pressure were at 40, 49, and 61 mm Hg. Estimates are adjusted for age, sex, and competing risk of mortality.

Table 2. Cox Proportional Hazards Models for Pulse Pressure and Mean Arterial Pressure as Predictors of Development of Atrial Fibrillation

Model	Covariates	Blood Pressure Component	Hazard Ratio* (95% Confidence Interval)	P Value
1	Age, sex	Pulse pressure	1.34 (1.22-1.47)	<.001
2	Model 1 plus initial body mass index, smoking, prevalent valvular disease, myocardial infarction, heart failure, diabetes, electrocardiographic left ventricular hypertrophy, and hypertension treatment	Pulse pressure	1.24 (1.11-1.39)	<.001
		Mean arterial pressure	1.00 (0.92-1.08)	.92
3	Model 2 plus time-dependent body mass index, smoking, valvular disease, myocardial infarction, heart failure, diabetes, electrocardiographic left ventricular hypertrophy and hypertension treatment	Pulse pressure	1.26 (1.12-1.43)	<.001
		Change in pulse pressure	1.09 (0.97-1.22)	.14
		Mean arterial pressure	0.96 (0.88-1.05)	.39
		Change in mean pressure	0.98 (0.90-1.06)	.64

*Hazard ratios expressed per 20 mm Hg for pulse pressure and per 10 mm Hg for mean arterial pressure.

Secondary Analyses

The association between baseline pulse pressure and incident AF did not vary significantly by age, sex, or presence of obesity ($P>.05$ for the interaction terms if added to model 2 of Table 2). We also evaluated pulse pressure as a categorical variable by creating pulse pressure groups based on approximate quartiles. Increasing pulse pressure category was significantly predictive of incident AF in this model (HR, 1.19 for the trend across the 4 pulse pressure groups; 95% CI, 1.08-1.31; $P<.001$).

COMMENT

Our study evaluated relations between pulse pressure and incident AF during 2 decades of prospective follow-up in the Framingham original and

offspring cohorts and showed that pulse pressure is an important predictor of incident AF even after considering other clinical variables known to be associated with AF (including baseline echocardiographic measures of left atrial size, left ventricular mass, and left ventricular fractional shortening). Thus, arterial stiffness, as evidenced by elevated pulse pressure, represents a potentially modifiable risk factor for AF.

Our analysis of the components of blood pressure indicates that the relation between blood pressure and incident AF is potentially related specifically to the pulsatile component of blood pressure as assessed by pulse pressure. Incident AF was unrelated to mean arterial pressure. Furthermore, model fit improved significantly if both systolic and diastolic blood pressures were considered together as compared with either being considered alone. These findings underscore a potential weakness of simply concentrating on systolic pressure and ignoring diastolic and pulse pressure. Our data suggest that systolic and diastolic pressure should be considered together, or more logically, pulse pressure should be considered if interpreting blood pressure relations with various end points including risk for developing AF.

Elevated pulse pressure, a surrogate measure for increased proximal aortic stiffness,²⁹ is associated with advancing age, higher body mass index, and prevalent diabetes, as was evident in our sample (Table 1). In addition, elevated pulse pressure predisposes to myocardial infarction,³⁰ heart failure,³¹ left ventricular hypertrophy,¹² impaired ventricular relaxation,¹³⁻¹⁵ and increased left atrial size.¹⁶ In our multivariable models, the association between pulse pressure and AF risk persisted in models that included echocardiographic left ventricular mass, left ventricular fractional shortening, left atrial size, time-dependent change in electrocardiographic left ventricular hypertrophy, and other established strong risk factors for AF. Our analysis, including time-dependent change in electrocardiographic left ventricular hy-

Table 3. Cox Proportional Hazards Models for Components of Blood Pressure as Predictors of Development of Atrial Fibrillation*

Blood Pressure Component	Hazard Ratio (95% Confidence Interval)†	P Value	-2 Log Likelihood
Diastolic pressure	0.97 (0.88-1.06)	.44	10561.3
Change in diastolic pressure	0.98 (0.90-1.06)	.56	
Mean arterial pressure	1.05 (0.97-1.13)	.26	10561.4
Change in mean arterial pressure	1.01 (0.94-1.09)	.75	
Systolic pressure	1.14 (1.04-1.25)	.006	10554.4
Change in systolic pressure	1.05 (0.97-1.14)	.27	
Pulse pressure	1.23 (1.11-1.37)	<.001	10548.0
Change in pulse pressure	1.08 (0.98-1.19)	.14	
Systolic pressure	1.23 (1.11-1.37)	<.001	10547.7
Change in systolic pressure	1.07 (0.98-1.18)	.15	
Diastolic pressure	0.87 (0.78-0.96)	.01	
Change in diastolic pressure	0.95 (0.86-1.05)	.28	10547.2
Pulse pressure	1.23 (1.11-1.37)	<.001	
Change in pulse pressure	1.08 (0.98-1.19)	.14	
Diastolic pressure	0.96 (0.88-1.05)	.39	
Change in diastolic pressure	0.98 (0.90-1.06)	.64	

*All models include age, sex, and time-dependent body mass index, smoking, valvular disease, myocardial infarction, heart failure, diabetes, electrocardiographic left ventricular hypertrophy, and hypertension treatment.

†Hazard ratios expressed per 20 mm Hg for systolic and pulse pressure and per 10 mm Hg for diastolic and mean arterial pressure.

pertrophy (shown to predict incident AF),³² suggests that increased risk for AF associated with elevated pulse pressure cannot be explained fully by changes in electrocardiographic left ventricular hypertrophy.

Episodic increases in systolic and pulse pressure in individuals with a stiff aorta may contribute to relations between pulse pressure and incident AF independently of effects on left atrial size or left ventricular mass. Acute increases in pulsatile load likely increase left atrial distending pressure, which may provide the substrate for initiation of AF.^{33,34} Alternatively, our relatively simple measure of left atrial dimension at baseline may inadequately characterize the full impact of elevated pulse pressure on left atrial structure and function³⁵ or the elevation of pulse pressure may antedate left atrial enlargement. Importantly, regardless of whether increased pulse pressure induces a substrate conducive to development of sustained AF through effects on atrial or ventricular structure or function, interventions known to reduce pulse pressure, such as blockade of the renin-angiotensin system, have been shown to reduce the incidence of new or recurrent AF.³⁶ Thus, increased pulse

pressure and the downstream pathways leading from elevated pulse pressure to AF are potentially reversible.

There are several alternative mechanisms whereby elevated pulse pressure could be associated with increased risk for AF. Pulse pressure may be a surrogate for age or elevated blood pressure, which are known risk factors for AF. However, our multivariable models adjusted for age, hypertension requiring treatment, and observed mean arterial pressure. Furthermore, we have shown that pulse pressure is the single blood pressure component most predictive of future development of AF. Indeed, mean arterial pressure considered alone or in combination with pulse pressure was unrelated to development of AF. Thus, the pulsatile component of blood pressure appears to be specifically related to risk for developing AF. Various cardiovascular disease risk factors predispose to arterial stiffening and increase the risk for AF. However, our analyses, which included clinical risk factors (age, diabetes, obesity, and smoking) as covariates, indicate that pulse pressure conveys additional risk for AF beyond the risk that is attributable to

these risk factors. Other potential mechanisms include the possibility that increased pulse pressure predisposes to neurohormonal activation^{37,38} or a generalized cardiovascular inflammatory response,^{39,40} which, in turn may contribute to the development of AF.⁴¹

Several potential limitations of our study merit consideration. We evaluated echocardiographic measures at a single examination. Consideration of change in echocardiographic measures over time during follow-up may have provided more robust prediction of risk for incident AF and may have indicated that increased risk for AF associated with elevated pulse pressure is mediated by subsequent effects of elevated pulse pressure on cardiac structure or function. We lacked power to analyze paroxysmal vs chronic AF or atrial flutter separately, so cannot comment if pulse pressure was more specifically related to subgroups of individuals with AF. Also, our cohort is predominantly white, middle-aged to elderly, and has normal or moderate elevations of blood pressure; thus, our findings may not be generalizable to younger individuals, other races/ethnicities, or individuals with severe hypertension. Finally, whereas the HRs associated with pulse pressure were statistically significant, the estimated effect size was modest. It remains to be determined whether interventions that alter pulse pressure will alter AF risk.

In summary, we have shown that increased pulse pressure, a simple and readily accessible if somewhat indirect measure of arterial stiffness, is likely an important risk factor for development of AF in a community-based sample. Arterial stiffness increases with advancing age, even in a relatively healthy sample.¹¹ However, increased arterial stiffness with advancing age is not inevitable and appears to be modifiable.⁴² As a result, increased arterial stiffness may represent a major modifiable risk factor for development of AF. Given the aging of the population, further research is needed to determine whether interventions aimed at reducing pulse pressure or preventing the increase in pulse pressure with

advancing age effectively reduce the incidence of AF. In light of the variable and often substantial increase in pulse pressure that accompanies advancing age, lifestyle modifications or therapy aimed specifically at reducing or limiting the increase in pulse pressure with advancing age may markedly reduce the substantial and rapidly growing incidence of AF in our aging society.

Author Contributions: Dr Mitchell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Levy and Benjamin are both senior authors on this article.

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Acquisition of data: Vasani, Wang, D'Agostino, Kannel, Benjamin.

Analysis and interpretation of data: Mitchell, Vasani, Keyes, Parise, Wang, Larson, D'Agostino, Kannel, Benjamin, Levy.

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Septicism the tonic of minds, the tonic of life, the agent
of truth—the way of art and salvation.
—Joseph Conrad (1857-1924)