

# Increased Pulse Pressure Independently Predicts Incident Atrial Fibrillation in Patients With Type 2 Diabetes

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**OBJECTIVE**—To examine whether baseline pulse pressure (PP), a marker of arterial stiffness, is associated with subsequent development of atrial fibrillation (AF) in type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—A total of 350 type 2 diabetic patients, who were free from AF at baseline, were followed for 10 years. A standard electrocardiogram was performed annually and a diagnosis of incident AF was confirmed in affected participants by a single cardiologist.

**RESULTS**—During the follow-up, 32 patients (9.1% of total) developed incident AF. After adjustments for age, sex, BMI, diabetes duration, presence of left ventricular hypertrophy, hypertension treatment, kidney dysfunction, and pre-existing history of coronary heart disease, heart failure, and mild valvular disease, baseline PP was associated with an increased incidence of AF (adjusted odds ratio 1.76 for each SD increment [95% CI 1.1–2.8];  $P < 0.01$ ).

**CONCLUSIONS**—Our findings suggest that increased PP independently predicts incident AF in patients with type 2 diabetes.

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**A**trial fibrillation (AF) is the most common sustained arrhythmia and contributes to substantial increases in morbidity and mortality (1–3). Increased pulse pressure (PP), a marker of arterial stiffness, has been reported to be an important predictor of new-onset AF in U.S. adults, independently of several clinical AF risk factors (4). In this prospective, observational study, we tested the hypothesis that baseline PP predicts subsequent development of incident AF in patients with type 2 diabetes.

## RESEARCH DESIGN AND

**METHODS**—A total of 350 type 2 diabetic outpatients, who were free from AF at baseline, were followed for 10 years. They were randomly selected among those who regularly attended our diabetes clinic during 2000–2001 ( $n = 1,918$ ) after

exclusion of those who had a history of AF, atrial flutter, hyperthyroidism, or moderate-to-severe valvular heart disease and those who were taking antiarrhythmic drugs. Participants were seen every 6–12 months for medical examinations of glycemic control, chronic diabetes complications, and routine electrocardiograms (ECGs). The ascertainment at the end of follow-up (January 2011) for the sample was 100%. The local ethics committee approved the study protocol. All participants gave their informed consent.

Pre-existing history of coronary heart disease, congestive heart failure (CHF), and mild valvular heart disease was confirmed by reviewing hospital medical records, including diagnostic symptoms patterns, echocardiograms, and other laboratory results. Presence of left ventricular hypertrophy (LVH) was diagnosed on the basis of a

standard 12-lead ECG according to Sokolow-Lyon voltage criteria and/or Cornell voltage criteria (5).

During the follow-up, participants were diagnosed with AF if AF or atrial flutter was present on an ECG that was obtained from hospital or physician chart or from a routine clinic examination in our clinic (i.e., a 12-lead ECG was performed yearly in all participants. A single, experienced cardiologist, who was blinded to subjects' details, confirmed the diagnosis of incident AF in affected participants.

## Statistical analysis

One-way ANOVA, the Kruskal-Wallis test, and the  $\chi^2$  test were used to compare the baseline characteristics of participants stratified by tertiles of baseline PP. Multivariate logistic regression analysis was used to separately examine the independent associations between the various components of blood pressure (systolic blood pressure, PP, or mean blood pressure, which were included in separate regression models as continuous variables, i.e., per 1-SD increment in each variable) and incident AF.

**RESULTS**—In the whole sample, age, diabetes duration, and A1C averaged 63 years, 6 years, and 7.7 %, respectively. Mean (SD) values of systolic blood pressure, PP, and mean blood pressure were  $140 \pm 15.2$ ,  $59.1 \pm 12.8$ , and  $100.7 \pm 8.8$  mmHg, respectively. Baseline characteristics of participants stratified by PP tertiles are displayed in Table 1.

During the follow-up of 10 years, 32 (9.1%) participants developed incident AF. The cumulative incidence of AF increased incrementally across PP tertiles (Table 1). In univariate analyses, each SD increment in PP (odds ratio [OR] 2.10 [95% CI 1.4–3.0]), systolic blood pressure (1.79 [1.2–2.6]) or mean blood pressure (1.43 [1.0–2.2]) was significantly associated with an increase in the risk of developing AF. After adjustment for age, sex, diabetes duration, electrocardiographic LVH, and hypertension

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Table 1—Baseline clinical and biochemical characteristics of the sample stratified by tertiles of PP

	1° tertile (PP <53 mmHg)	2° tertile (PP 53–60 mmHg)	3° tertile (PP >60 mmHg)	P
Sex (male/female), n/n	67/59	69/47	61/47	0.61
Age (years)	59 ± 10	63 ± 10	68 ± 9	<0.0001
BMI (kg/m <sup>2</sup> )	29.7 ± 4	30.2 ± 5	29.3 ± 5	0.22
Diabetes duration (years)	5.4 ± 6.5	7.5 ± 7.5	8.4 ± 8.8	<0.01
Systolic blood pressure (mmHg)	125 ± 10	140 ± 8	156 ± 9	<0.0001
Diastolic blood pressure (mmHg)	80 ± 8	81 ± 8	81 ± 7	0.33
Mean blood pressure (mmHg)	95 ± 9	101 ± 8	106 ± 7	<0.0001
A1C (%)	7.6 ± 1.7	7.9 ± 1.9	7.7 ± 1.5	0.26
Total cholesterol (mmol/L)	5.25 ± 0.9	5.18 ± 1.0	5.23 ± 1.0	0.79
HDL cholesterol (mmol/L)	1.18 ± 0.3	1.20 ± 0.3	1.26 ± 0.3	0.13
LDL cholesterol (mmol/L)	3.36 ± 0.8	3.19 ± 0.8	3.36 ± 0.7	0.21
Triglycerides (mmol/L)	1.75 ± 0.9	1.81 ± 0.9	1.63 ± 0.8	0.30
Hypertension	48.4	73.3	86.1	<0.0001
Electrocardiographic LVH	9.5	16.4	32.4	<0.0001
Current smokers	25.4	24.1	20.4	0.06
History of coronary heart disease	7.9	11.2	13.0	0.57
History of CHF	0.8	2.6	3.7	0.33
History of mild valvular heart disease	0.9	1.5	0.9	0.86
Chronic kidney disease	16.7	31.0	27.8	0.12
Diabetic retinopathy	24.3	21.4	24.5	0.66
Lower-limb sensory neuropathy	23.0	11.3	23.3	0.08
ACE inhibitors or sartans	42.9	68.9	73.1	<0.0001
Calcium channel blockers	13.5	25.0	43.5	<0.0001
α-Blockers	6.3	2.6	11.1	<0.05
β-Blockers	13.5	16.4	12.0	0.77
Diuretics	25.4	31.9	37.9	0.22
Antiplatelet drugs	52.8	43.3	62.8	0.25
Lipid-lowering drugs	19.1	32.8	22.2	0.20
Oral hypoglycemic drugs	75.4	85.3	83.3	0.63
Insulin therapy	18.2	28.4	23.1	0.50
Incidence rate of AF	2.6	9.5	15.7	<0.0001

Data are means ± SD or percentages unless otherwise indicated. Cohort size,  $n = 350$ . PP was calculated as the difference between systolic and diastolic blood pressure.  $P$  values for trends were determined by means of one-way ANOVA, Kruskal-Wallis test (for continuous variables not normally distributed, i.e., diabetes duration and triglycerides), and  $\chi^2$  test (for categorical variables). Hypertension was defined as blood pressure  $\geq 140/90$  mmHg or use of any antihypertensive drug treatment. LVH was diagnosed according to Sokolow-Lyon voltage criteria (SV1 + RV5 or RV6  $\geq 3.5$  mV) and/or Cornell voltage criteria (SV3 + RaVL  $> 2.0$  mV in women and  $> 2.8$  mV in men). Chronic kidney disease was defined as the presence of abnormal albuminuria (albumin-to-creatinine ratio  $\geq 30$   $\mu\text{g}/\text{mg}$ ) and/or glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup> as estimated by the four-variable Modification of Diet in Renal Disease study equation. Diabetic retinopathy was diagnosed by funduscopy, and lower-limb sensory neuropathy was diagnosed by biothesiometer.

treatment, only PP maintained a significant association with incident AF (adjusted OR 1.71 [1.1–2.7],  $P < 0.01$ ). In contrast, the associations of systolic blood pressure (1.46 [0.9–1.9]) and mean blood pressure (1.21 [0.7–1.5]) with incident AF were no longer significant after adjusting for the above-mentioned covariates. Results remained unchanged even after exclusion of those who improved their PP values during the follow-up (~40% of patients changed baseline PP tertiles during follow-up). In a less parsimonious

regression model, the significant association between PP and incident AF persisted after additional adjustment for BMI, chronic kidney disease, and history of previous coronary heart disease, CHF, and mild valvular disease (1.76 [1.1–2.8],  $P < 0.01$ ). However, given the number of clinical outcomes ( $n = 32$ ), the results of this regression model should be interpreted with some caution. Notably, other independent predictors of incident AF were older age, LVH, and history of CHF ( $P < 0.001$ ).

**CONCLUSIONS**—This is the first study to specifically examine the role of PP in predicting development of incident AF in type 2 diabetic individuals, who were free from AF at baseline. The major finding of this study was that increased PP predicted incident AF during 10 years of follow-up, independently of LVH and other clinical AF risk factors. In contrast, systolic blood pressure and mean blood pressure were not independently associated with incident AF.

Our results complement and expand recent findings from the Framingham Heart Study demonstrating that baseline PP is an independent risk factor for new-onset AF in the community (4). It is remarkable to note that both in the Framingham Heart Study and in our study, the analysis of the components of blood pressure indicates that the relationship between blood pressure and incident AF is potentially related specifically to the age-related pulsatile component of blood pressure as assessed by PP. The increase in PP adds significantly to the pulsatile load of blood pressure on the heart (6), thereby promoting LVH (7), impaired LV diastolic relaxation (8–10), and left atrial enlargement (11). Strong evidence supports the concept of increased arterial stiffness in people with type 2 diabetes (12–14).

Our study has some important limitations. First, because our sample comprised white type 2 diabetic individuals, who were followed at an outpatient diabetes clinic, our results may not necessarily be generalizable to other nonwhite diabetic populations. Second, we measured PP, which is a simple and readily accessible if somewhat indirect measure of arterial stiffness. Third, the diagnosis of LVH was based on widely accepted ECG criteria (that have a specificity of 98–100% but a sensitivity of 30–40% compared with echocardiographic findings); echocardiography for detecting LVH at baseline was available only for few patients. Finally, there were also a relatively small number of clinical events during the follow-up; therefore, the results should be interpreted with some caution.

In conclusion, our results suggest that elevated PP is associated with an increased incidence of AF in type 2 diabetic patients, independently of several AF clinical risk factors. Further studies are needed to confirm this finding and to explore whether pharmacological interventions aimed at reducing PP or preventing the increase in PP with advancing age effectively reduce the incidence of AF in type 2 diabetic patients.

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F.V. researched data, contributed to discussion, and wrote the manuscript. S.B. and G.A. contributed to discussion and reviewed and edited the manuscript. L.B. and L.Z. researched data and reviewed and edited the manuscript. G.T. researched data, analyzed data, and wrote the manuscript. G.T. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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