The goal of this study was to evaluate the impact of hypertension on the outcome of atrial fibrillation (AF) ablation.

Hypertension is a well-known independent risk factor for incident AF. Controlled hypertension does not affect the AF ablation outcome when compared with patients without hypertension. By contrast, uncontrolled hypertension confers higher AF recurrence risk and requires more extensive ablation.

After adjusting for confounders, uncontrolled hypertension (group I) (hazard ratio [HR]: 1.52, p = 0.001), and non-PV triggers (HR: 1.85, p = 0.003). Among patients in group I who underwent additional non-PV trigger ablation, freedom from AF/atrial tachycardia was 69.8%, which was similar to groups II and III procedural success (log-rank p = 0.7). After adjusting for confounders, uncontrolled hypertension (group I) (hazard ratio [HR]: 1.52, p = 0.045), non-PV triggers (HR: 1.85, p < 0.001), and nonparoxysmal AF (HR: 1.64, p = 0.002) demonstrated significant association with arrhythmia recurrence.

Conclusions: Controlled hypertension does not affect the AF ablation outcome when compared with patients without hypertension. By contrast, uncontrolled hypertension confers higher AF recurrence risk and requires more extensive ablation.

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OBJECTIVES The goal of this study was to evaluate the impact of hypertension on the outcome of atrial fibrillation (AF) ablation.

BACKGROUND Hypertension is a well-known independent risk factor for incident AF.

METHODS A total of 531 consecutive patients undergoing AF ablation were enrolled in this study and divided into three groups: patients with uncontrolled hypertension despite medical treatment (group I, n = 160), patients with controlled hypertension (group II, n = 192), and patients without hypertension (group III, n = 179). Pulmonary vein (PV) antrum and posterior wall isolation was always performed, and non-PV triggers were identified during isoproterenol infusion. All patients underwent extensive follow-up.

RESULTS Three groups differed in terms of left atrial (LA) size, non-PV triggers, and moderate/severe LA scar. Non-PV triggers were present in 94 (58.8%), 64 (33.3%), and 50 (27.9%) patients in groups I, II, and III, respectively (p < 0.001). After 19 ± 7.7 months of follow-up, 65 (40.6%), 54 (28.1%), and 46 (25.7%) patients in groups I, II, and III had recurrences (log-rank test, p = 0.003). Among patients in group I who underwent additional non-PV trigger ablation, freedom from AF/atrial tachycardia was 69.8%, which was similar to groups II and III procedural success (log-rank p = 0.7). After adjusting for confounders, uncontrolled hypertension (group I) (hazard ratio [HR]: 1.52, p = 0.045), non-PV triggers (HR: 1.85, p < 0.001), and nonparoxysmal AF (HR: 1.64, p = 0.002) demonstrated significant association with arrhythmia recurrence.

CONCLUSIONS Controlled hypertension does not affect the AF ablation outcome when compared with patients without hypertension. By contrast, uncontrolled hypertension confers higher AF recurrence risk and requires more extensive ablation.
Atrial fibrillation (AF) and hypertension are 2 distinct, but often related, cardiovascular diseases with a high and increasing incidence in the overall population (1,2). Arterial hypertension is a well-known independent risk factor for AF (3), a risk that is increased especially when hypertension is uncontrolled (4). The risk of AF in hypertensive compared with normotensive subjects was increased by 1.9 times in the Framingham Heart Study (5) and 1.4 times in the Manitoba Follow-Up Study (6).

The role of different antihypertensive drugs in reducing the risk of incident atrial fibrillation has been investigated in several studies (7,8), and only when therapy is targeted at regression or prevention of electrocardiographic left ventricular (LV) hypertrophy may the incidence of new-onset AF be reduced (9).

In the context of AF catheter ablation through pulmonary vein antrum isolation (PVAI) (10), hypertension represents one of the main pre-procedural risk factors for AF recurrence (11), but the impact of uncontrolled hypertension on AF ablation outcome has not yet been established.

The main scope of this study is to investigate first whether uncontrolled hypertension plays a role in AF recurrence and, second, which is the best ablation strategy in these patients.

METHODS

STUDY POPULATION. A total of 531 consecutive patients undergoing their first AF catheter ablation were enrolled in this prospective study. Patients were classified into 3 groups: patients with uncontrolled hypertension despite medical treatment (group I, n = 160), patients with controlled hypertension through medical therapy (group II, n = 192), and patients without hypertension (group III, n = 179).

Standard definitions of paroxysmal, persistent, and long-standing persistent AF were used (12). AF type was categorized into 2 main groups for the study purpose: paroxysmal atrial fibrillation (PAF) and nonparoxysmal atrial fibrillation (NPAF), which included persistent and long-standing persistent AF.

The definition of hypertension followed the 2013 ESH/ESC Guidelines for the Management of Arterial Hypertension (13) and the ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly (14).

DEFINITION OF UNCONTROLLED HYPERTENSION. Patients who were treated with 3 or more antihypertensive drugs and came to our observation with a history of uncontrolled hypertension were considered to have uncontrolled hypertension. Blood pressure (BP) was measured 3 times during our medical evaluation (1 week before ablation) at rest in the sitting position, separated by at least 5 min, and then the readings were averaged. If BP values were higher than the upper normal limit, patients were included in group I, otherwise the patients were included in group II. The upper normal limits for the systolic and diastolic BP were 140 mm Hg and 90 mm Hg, respectively.

Patients with secondary hypertension were excluded, for example, patients with a history of renal disease, pheochromocytoma, hyperaldosteronism, thyroid disease, and drug/substance intake (oral contraceptives, carbinoxolone, vasoconstrictive nasal drops, cocaine, amphetamines, gluco- and mineralocorticoids, nonsteroidal anti-inflammatory drugs, erythropoietin, cyclosporine) (13).

Participating centers in the study were: 1) Texas Cardiac Arrhythmia Institute, St. David Medical Center, Austin, Texas; 2) California Pacific Medical Center, San Francisco, California; 3) Scripps Clinic, San Diego, California; 4) University of Kentucky, Lexington, Kentucky; 5) University of Kansas, Kansas City, Kansas; 6) Akron General Hospital, Akron, Ohio; and 7) Cardiac Arrhythmia Research Centre, Centro Cardiologico Monzino, Milan, Italy.

All patients signed an informed written consent for the procedure.

ABLAITION PROCEDURE. Anti-arrhythmic drugs (AADs), with the exception of amiodarone, were discontinued 3 to 5 days before the procedure. Patients on amiodarone were asked to discontinue the drug 4 to 6 months before the ablation. Procedures were performed under general anesthesia using most commonly propofol (2 mg/kg), fentanyl (1 to 2 µg/kg), and rocuronium (0.5 to 1.0 mg/kg).

PVAI AND POSTERIOR WALL ABLATION. All patients underwent PVAI and posterior wall isolation. PVAI has been described in detail elsewhere (15,16). Briefly, we used a circular mapping catheter (Lasso, Biosense Webster, Johnson & Johnson, Diamond Bar, California) and a 3.5-mm irrigated tip catheter (ThermoCool, Biosense Webster) to ablate the antrum of the pulmonary veins (PVs) and to achieve abolition of all electrograms.

Intracardiac echocardiography was used to monitor the transseptal puncture and to define the anatomy of the PVs. An esophageal probe was used to
monitor the temperature in the esophagus during ablation.

Radiofrequency (RF) energy output was titrated to a maximum of 45 W while maintaining a catheter tip temperature of \( \leq 41^\circ C \). At each site, energy was delivered for 20 s. The maximum power over the esophagus was limited to 30 W, and energy delivery was discontinued when the esophageal temperature probe reached \( 39^\circ C \).

The procedural endpoint for this ablation strategy was the local elimination of all the PV potentials along the antra or inside the veins (entry and exit block). The antrum included the entire posterior wall and extended anteriorly to the right PVs along the left septum.

If AF termination was not achieved, cardioversion was performed, and when AF organized into an atrial tachycardia (AT), the latter arrhythmia was mapped and ablated. During sinus rhythm, isoproterenol administration up to 30 \( \mu \text{g/min} \) was started for 15 to 20 min to check for PV reconnection and any firing sites outside the PV antrum.

**Ablation of Non-PV Triggers.** On the basis of operator choice, the presence of sustained or not sustained arrhythmias including premature atrial complexes, arising outside the PV antrum, during isoproterenol infusion, were ignored (group Ib, group IIb, and group IIIb for subgroups of groups I, II, and III, respectively) or targeted (group Ia, group IIa, and group IIIa for subgroups of groups I, II, and III, respectively) during ablation. Non-PV triggers were defined as any firing sites outside the PV antrum.

The origin of these triggers was assessed by combining the 12-lead electrocardiogram morphology of the premature atrial complexes inducing AF and the earliest local intracardiac bipolar electrograms recorded on the catheter dipoles (17,18). One circular 20-pole catheter was placed in the left superior PV and the other in the right superior vena cava. The duodecapolar linear catheter was recording the coronary sinus and the inferior and posterior areas of the right atrium.

The procedural endpoint for this ablation strategy was the electrical isolation of all PVs, including the posterior wall, and the ablation of sustained or not sustained premature atrial complexes arising outside the PV antrum, induced during isoproterenol infusion.

**Left Atrial Mapping and Definition of Scar.** Before PVAI, all patients underwent detailed voltage mapping of the left atrium (LA). Mapping was always performed in sinus rhythm whenever possible. All patients in both groups had electroanatomic mapping of the LA performed using the CARTO 3D system (Biosense Webster). LA mapping was performed using point-by-point acquisition with the Navistar ThermoCool or ThermoCool SF catheter (Biosense Webster; 3.5-mm distal tip electrode, 2-mm ring electrode with interelectrode distance of 1 mm). At least 100 points, homogenously distributed, were taken to create the entire chamber. A denser sampling of the posterior LA and PV antrum was performed.

To ensure adequate catheter-tissue contact, a combination of intracardiac echocardiography, orthogonal fluoroscopy, and electrogram characteristics was used. Whenever computed tomography- or magnetic resonance imaging-segmented LA anatomy was available, it was merged with the electroanatomic map.

Bipolar signals were recorded between the distal electrode pair (filtered at 30 to 400 Hz). The CARTO system automatically uses peak-to-peak bipolar electrograms amplitude for measurement. Each point acquired on the LA voltage map was reviewed manually to exclude PV potentials, noise, or pacing artifacts.

Scar was defined as the absence of voltage or a bipolar voltage amplitude \( \leq 0.05 \text{ mV} \) indistinguishable from noise. After an accurate evaluation of the LA voltage map, we classified LA scar according to the percentage of the estimated LA scar area involved as mild (<20%), moderate (20% to 60%), or severe (>60%).

**Follow-up.** After overnight observation following ablation, patients were discharged on their previously ineffective AADs, which were continued during the blanking period (12 weeks). After the blanking period, AADs were discontinued. In case of recurrence after the blanking period, patients were given either previously ineffective AADs or new antiarrhythmic agents, or were scheduled for repeat ablation.

Follow-up was performed at 3, 6, 9, 12, 18, and 24 months after the procedure, with cardiology evaluation, 12-lead electrocardiogram, and 7-day Holter monitoring. Patients were given an event recorder for the first 5 months after ablation and were asked to transmit their rhythm every time they had symptoms compatible with arrhythmias and at least twice a week even if asymptomatic.

**Primary Endpoint.** The primary endpoint of this study was freedom from AF defined as no episodes of AF/AT with or without AADs that lasted more than 30 s at follow-up. Episodes that occurred during the first 3 months (blanking period) after the procedure were not considered as recurrences.
**STATISTICAL ANALYSIS.** Continuous data were described as mean ± SD, and categorical data as counts and percentages. Student t test, analysis of variance, chi-square test, and Fisher exact test were used to compare differences across groups. If there was significant difference between the groups, then post-hoc multiple pairwise group comparison was performed by the Bonferroni method. A multivariable Cox regression analysis was used for identifying significant predictors of AF or AT recurrence while controlling for clinically relevant covariates. All potential confounders were entered into the model on the basis of known clinical relevance or significance observed in univariate analysis. Variables included in the model were age, sex, study group, diabetes, coronary artery disease, dyslipidemia, LA size >4 cm, non-PV triggers, and type of AF. Group III (without hypertension) was used as the reference group to determine the impact of group I and group II on recurrence. Tests were run to examine the presence of interaction, multicollinearity, and proportional hazard. The hazard ratio (HR) and 95% confidence interval of AF recurrence were calculated. Time to event was calculated in months from the ablation procedure date to the date of recurrence. Recurrence-free survival over time was calculated by the Kaplan-Meier method. The log-rank test was used to compare survival distribution across groups, and if significant, then multiple pairwise comparison by Sidák correction was used. All tests were 2-sided, and a p value <0.05 was considered statistically significant. Analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina) and IBM SPSS Statistics 21.0 (IBM SPSS, Chicago, Illinois).

**RESULTS**

**PATIENTS CHARACTERISTICS.** Baseline characteristics of the 3 groups are presented in Table 1. Mean age of the study population was 64.5 ± 9.6 years, with 370 (69.7%) male and 352 (66.3%) paroxysmal AF patients. All the groups were similar in terms of age, sex, LV ejection fraction, dyslipidemia, diabetes, and percentages. Student t test, analysis of variance, chi-square test, and Fisher exact test were used to compare differences across groups. If there was significant difference between the groups, then post-hoc multiple pairwise group comparison was performed by the Bonferroni method. A multivariable Cox regression analysis was used for identifying significant predictors of AF or AT recurrence while controlling for clinically relevant covariates. All potential confounders were entered into the model on the basis of known clinical relevance or significance observed in univariate analysis. Variables included in the model were age, sex, study group, diabetes, coronary artery disease, dyslipidemia, LA size >4 cm, non-PV triggers, and type of AF. Group III (without hypertension) was used as the reference group to determine the impact of group I and group II on recurrence. Tests were run to examine the presence of interaction, multicollinearity, and proportional hazard. The hazard ratio (HR) and 95% confidence interval of AF recurrence were calculated. Time to event was calculated in months from the ablation procedure date to the date of recurrence. Recurrence-free survival over time was calculated by the Kaplan-Meier method. The log-rank test was used to compare survival distribution across groups, and if significant, then multiple pairwise comparison by Sidák correction was used. All tests were 2-sided, and a p value <0.05 was considered statistically significant. Analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina) and IBM SPSS Statistics 21.0 (IBM SPSS, Chicago, Illinois).

**TABLE 1 Baseline Population Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 160)</th>
<th>Group II (n = 192)</th>
<th>Group III (n = 179)</th>
<th>Overall p Value</th>
<th>Group III vs. Group I</th>
<th>Group III vs. Group II</th>
<th>Group I vs. Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>112 (70)</td>
<td>125 (65.1)</td>
<td>133 (74.3)</td>
<td>0.16</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Age, yrs</strong></td>
<td>65.4 ± 7.8</td>
<td>64.4 ± 9.7</td>
<td>63.7 ± 10.80</td>
<td>0.29</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>30.8 ± 5.4</td>
<td>30.9 ± 7.7</td>
<td>30.02 ± 5.40</td>
<td>0.35</td>
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<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>16 (10)</td>
<td>15 (7.8)</td>
<td>15 (8.4)</td>
<td>0.76</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dyslipidemia</td>
<td>55 (34.4)</td>
<td>64 (33.3)</td>
<td>56 (31.3)</td>
<td>0.80</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CAD</td>
<td>38 (23.8)</td>
<td>41 (21.4)</td>
<td>21 (11.7)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.039</td>
<td>1.00</td>
</tr>
<tr>
<td>History of stroke/TIA</td>
<td>12 (7.5)</td>
<td>13 (6.8)</td>
<td>11 (6.2)</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>6 (3.8)</td>
<td>6 (3.1)</td>
<td>8 (4.5)</td>
<td>0.79</td>
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<td></td>
<td></td>
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<tr>
<td><strong>Type of AF</strong></td>
<td></td>
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</tr>
<tr>
<td>PAF</td>
<td>109 (68.1)</td>
<td>126 (65.6)</td>
<td>117 (65.4)</td>
<td>0.84</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>NPAF</td>
<td>51 (31.9)</td>
<td>66 (34.4)</td>
<td>62 (34.6)</td>
<td>0.84</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pre-procedure echocardiographic parameters</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LAD, mm</td>
<td>44.1 ± 5.5</td>
<td>42.7 ± 5.4</td>
<td>41.0 ± 6.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.06</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55.9 ± 7.5</td>
<td>56.2 ± 8.9</td>
<td>56.9 ± 9.3</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Procedural parameters</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Moderate-to-severe LA scar</td>
<td>57 (35.6)</td>
<td>44 (22.9)</td>
<td>25 (14.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.081</td>
<td>0.026</td>
</tr>
<tr>
<td>Procedure time, min</td>
<td>156.6 ± 70.70</td>
<td>148.03 ± 43.20</td>
<td>148.15 ± 40.60</td>
<td>0.22</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fluoroscopy time, min</td>
<td>59.7 ± 24.1</td>
<td>55.18 ± 22.10</td>
<td>53.11 ± 20.4</td>
<td>0.02</td>
<td>0.02</td>
<td>1.00</td>
<td>0.17</td>
</tr>
<tr>
<td>Radiofrequency time, min</td>
<td>71.24 ± 30.50</td>
<td>69.39 ± 31.10</td>
<td>68.54 ± 28.90</td>
<td>0.71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-PV triggers</td>
<td>94 (58.8)</td>
<td>64 (33.3)</td>
<td>50 (27.9)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.78</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR</td>
<td>2.35 ± 0.30</td>
<td>2.39 ± 0.50</td>
<td>2.37 ± 0.60</td>
<td>0.74</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. *The significance presented is based on the multiplicity-corrected type I error.

BMI = body mass index; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; INR = international normalized ratio; LA = left atrial; LAD = left atrial diameter; LVEF = left ventricular ejection fraction; NPAF = nonparoxysmal atrial fibrillation; PAF = paroxysmal atrial fibrillation; PV = pulmonary vein; TIA = transient ischemic attack.
TABLE 2 BP Values Among Patients With Uncontrolled HTN (Group I) and Controlled (Group II)

<table>
<thead>
<tr>
<th>BP Values</th>
<th>Group I Uncontrolled HTN (n = 160)</th>
<th>BP Values</th>
<th>Group II Controlled HTN (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>140-149 mm Hg</td>
<td>120 mm Hg</td>
<td>94 (49.0)</td>
</tr>
<tr>
<td></td>
<td>150-159 mm Hg</td>
<td>120-129 mm Hg</td>
<td>67 (34.9)</td>
</tr>
<tr>
<td></td>
<td>160-169 mm Hg</td>
<td>130-139 mm Hg</td>
<td>94 (49.0)</td>
</tr>
<tr>
<td></td>
<td>≥170 mm Hg</td>
<td>7 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Average SBP, mm Hg</td>
<td>156.6 ± 7.4</td>
<td>127.7 ± 8.0</td>
<td></td>
</tr>
<tr>
<td>DBP</td>
<td>90-94 mm Hg</td>
<td>&lt;65 mm Hg</td>
<td>15 (7.8)</td>
</tr>
<tr>
<td></td>
<td>95-99 mm Hg</td>
<td>65-69 mm Hg</td>
<td>20 (10.4)</td>
</tr>
<tr>
<td></td>
<td>≥100 mm Hg</td>
<td>70-74 mm Hg</td>
<td>34 (17.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75-79 mm Hg</td>
<td>45 (23.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80-84 mm Hg</td>
<td>48 (25.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>85-89 mm Hg</td>
<td>30 (15.6)</td>
</tr>
<tr>
<td>Average DBP, mm Hg</td>
<td>94.9 ± 4.4</td>
<td>76.5 ± 7.5</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (%) or mean ± SD. BP = blood pressure; DBP = diastolic blood pressure; HTN = hypertension; SBP = systolic blood pressure.

Body mass index, history of stroke/transient ischemic attack, type of AF, and chronic obstructive pulmonary disease. Meanwhile, the 3 groups differed in terms of LA size (44.1 ± 5.5 mm, 42.7 ± 5.4 mm, and 41.0 ± 6.1 mm in groups I, II, and III, respectively), non-PV triggers (58.8%, 33.3%, and 27.9% in groups I, II, and III, respectively), moderate/severe LA scar (35.6%, 22.9%, and 14.0% in groups I, II, and III, respectively), and history of coronary artery disease (CAD) (23.8%, 21.4%, and 11.7% in groups I, II, and III, respectively).

With multiplicity-adjusted error rate, group I, compared with group III, had a larger LA diameter and higher prevalence of CAD, non-PV triggers, and moderate-to-severe LA scar. Similarly, group II had a larger LA diameter and more prevalence of CAD compared with group III, whereas group II’s prevalence of non-PV triggers and moderate-to-severe scar was not different from group III. Group I and group II did not differ in terms of LA diameter and CAD prevalence, whereas group I had more prevalence of non-PV triggers and moderate-to-severe scar. The baseline characteristics with pairwise group comparisons are presented in Table 1.

The mean duration of hypertension was 9 ± 6 years for the uncontrolled (group I) and 9 ± 7 years for the control group (group II). The mean systolic and diastolic BP in the uncontrolled group were 156.6 ± 7.4 mm Hg and 94.9 ± 4.4 mm Hg, respectively (Table 2). The majority of the patients had systolic BP between 150 and 159 mm Hg (60%), whereas almost one-half of the patients had diastolic BP between 90 and 94 mm Hg (53.1%). In the uncontrolled hypertension group, the average number of drugs per patient was 3.1 (Table 3).

The mean systolic and diastolic BP in the controlled group were 127.7 ± 8.0 mm Hg and 76.5 ± 7.5 mm Hg, respectively. In the controlled hypertension group, the average number of drugs per patient was 1.85 (Table 3).

**TABLE 3 Antihypertensive Medication Among Patients With Uncontrolled HTN (Group I) and Controlled (Group II)**

<table>
<thead>
<tr>
<th>Antihypertensive Medication</th>
<th>Group I Uncontrolled HTN (n = 160)</th>
<th>Group II Controlled HTN (n = 192)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting-enzyme inhibitor</td>
<td>97 (60.6)</td>
<td>63 (32.8)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>126 (78.8)</td>
<td>89 (46.4)</td>
</tr>
<tr>
<td>Diuretic agent</td>
<td>146 (91.3)</td>
<td>109 (56.8)</td>
</tr>
<tr>
<td>ARB</td>
<td>80 (50.0)</td>
<td>52 (27.1)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>37 (23.1)</td>
<td>29 (15.1)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (8.8)</td>
<td>13 (6.8)</td>
</tr>
<tr>
<td>Total number of drugs</td>
<td>500</td>
<td>355</td>
</tr>
<tr>
<td>Number of drugs per patient</td>
<td>3.1 (500 medications/n = 160)</td>
<td>1.85 (355 medications/n = 192)</td>
</tr>
</tbody>
</table>

Values are n (%). ARB = angiotensin II receptor blocker; HTN = hypertension.

**PROCEDURAL RESULTS.** The procedural endpoint was achieved for all patients in each group. Procedural time was 156.68 ± 70.7 min, 148.03 ± 43.2 min, and 148.15 ± 40.6 min (p = 0.02) for groups I, II, and III, respectively. The total fluoroscopy time was longer (p = 0.02) in group I, whereas RF time was similar (p = 0.7) in the 3 groups (Table 1). With multiplicity-adjusted error rate, group I, compared with group III, had a longer duration of fluoroscopy time and group II had a similar duration. There was no difference in fluoroscopy time between group I and group II.

**CHRONIC FOLLOW-UP/PRIMARY ENDPOINT.** After a mean follow-up of 19 ± 7.7 months, the primary endpoint of the study as freedom from AF/AT after a single procedure with or without AADs is reported in Figure 1. After this period of follow-up, 65 (40.6%), 54 (28.1%), and 46 (25.7%) patients in groups I, II, and III had recurrences (log-rank test, p = 0.003) (Figure 1).

**NON-PV TRIGGERS, AF ABLATION APPROACH, AND PROCEDURE OUTCOME.** After a mean follow-up of 19 ± 7.7 months, 95 (59.4%), 138 (71.9%), and 133 (74.3%) patients in group I, group II, and group III, respectively, achieved success after the first ablation.
procedure. Recurrence-free survival over time by Kaplan-Meier curves showed significant differences in survival between the 3 groups (log-rank test, \( p = 0.0035 \)). In multiple pairwise comparison by the Sidák correction method, the success rate in group I was significantly less compared with group II (\( p = 0.03 \)) and group III (\( p = 0.006 \)), although the success rates in group II and group III were similar (\( p = 0.96 \)) (Figure 1).

In group I, 94 patients had non-PV triggers at electrophysiological (EP) study, and on the basis of operator choice, 43 of 94 patients underwent non-PV trigger ablation (group Ia), whereas 51 of 94 did not undergo non-PV trigger ablation (group Ib). The

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**FIGURE 1**  Kaplan-Meier Curves of Freedom From Recurrent ATa for Different Groups After First Ablation

(A) The Kaplan-Meier curve for the 3 groups irrespective of the ablation strategy. (B) A comparison among patients of group I receiving additional non-pulmonary vein trigger ablation and group II and group III. (C) A comparison among patients of group I receiving standard PVAI ablation and group II and group III. ATa — atrial tachyarrhythmia; HTN — hypertension; NPV — non-pulmonary vein; PVAI — pulmonary vein antrum isolation.
success rates in group Ia and group Ib were 69.8% (30 of 43) and 37.3% (19 of 51), respectively. The success rate in group I patients without non-PV triggers at EP study was 69.7% (46 of 66). Interestingly, group I patients who underwent additional non-PV trigger ablation (group Ia) had similar recurrence-free survival over time as groups II and III (log-rank \( p = 0.7 \) (Figure 1B), whereas success was very low (37.3%) in group I patients in whom non-PV triggers were not ablated (group Ib) compared with group II and III (log-rank \( p < 0.001 \) (Figure 1C)).

In group II, 64 patients had non-PV triggers at EP study, and on the basis of operator choice, 29 of 64 patients underwent non-PV trigger ablation (group IIa), whereas 35 of 64 did not undergo non-PV trigger ablation (group IIb). The success rates in group IIa and IIb were 75.9% (22 of 29) and 45.7% (16 of 35), respectively. The success rate in group II patients without non-PV triggers was 78.1% (100 of 128).

Similarly, in group III, 50 patients had non-PV triggers at EP study, and based on operator choice, 23 of 50 patients underwent non-PV trigger ablation (group IIIa), whereas 27 of 50 did not undergo non-PV trigger ablation (group IIIb). The success rates in groups IIIa and IIIb were 78.3% (18 of 23) and 48.2% (13 of 27), respectively. The success rate in group III patients without non-PV triggers was 79.1% (102 of 129).

**Predictors of Arrhythmia Recurrence on Multivariate Analysis.** In univariate analysis, uncontrolled hypertension (HR: 1.79, \( p = 0.003 \)), non-PV trigger (HR: 2.13, \( p < 0.001 \)), and NPAF (HR: 1.72, \( p < 0.001 \)) were predictors of recurrence, whereas age (HR: 1.01, \( p = 0.17 \)), male sex (HR: 1.26, \( p = 0.16 \)), diabetes (HR: 1.23, \( p = 0.40 \)), CAD (HR: 1.3, \( p = 0.16 \)), and large LA size (>4 cm; HR: 1.12, \( p = 0.19 \)) did not associate with recurrence. Multivariable Cox proportional hazard analysis for recurrence-free survival was performed to analyze the association between procedure outcome and hypertension control. After adjusting for variables as described in the Methods section, the presence of uncontrolled hypertension (group I; HR: 1.52, \( p = 0.045 \)), non-PV triggers (HR: 1.85, \( p < 0.001 \)), and NPAF (HR: 1.64, \( p = 0.002 \)) demonstrated significant association with arrhythmia recurrence.

Furthermore, multivariable analysis was performed in PAF and NPAF separately. In NPAF patients (\( n = 179 \)), uncontrolled hypertension and non-PV triggers were associated with recurrence (HR: 2.59 [95% CI: 1.31 to 5.13] and 2.72 [95% CI: 1.54 to 4.81], respectively), whereas uncontrolled hypertension and non-PV triggers were unable to predict the recurrence in PAF patients (\( n = 352 \); HR: 1.02 [95% CI: 0.60 to 1.73] and 1.49 [95% CI: 0.96 to 2.32], respectively) (Table 4).

**Complications.** During ablation, cardiac effusion, resolved by pericardiocentesis, occurred in 2, 1, and 2 patients in groups I, II, and III, respectively (\( p = 0.74 \)), and groin hematoma occurred in 2, 1, and 1 patients in groups 1, 2, and 3, respectively (\( p = 0.69 \)) (Table 5).

**Discussion**

**Main Findings.** This is the first study to evaluate the role of uncontrolled hypertension in the context of AF ablation, its clinical and EP features, and the possible ablation strategy. Our results did not show any statistical difference in AF recurrence rate following ablation between patients with controlled hypertension and no hypertension, at the long-term follow-up. By contrast, pharmacologically uncontrolled hypertension confers higher AF recurrence risk and requires more extensive ablation. More non-PV triggers were identified in these patients, resulting in higher recurrence if ignored.

**AF and Hypertension.** Several studies have established hypertension to be an independent risk factor for AF. Upper limit of normal BP values are long-term predictors of AF in initially healthy middle-aged men (19) and women (20). Verdecchia et al. (21), in a population of hypertensive patients without

<table>
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<tr>
<th>Table 4: Multivariable Cox Analysis for ATa Recurrences After First Ablation for All the Patients and Subgroups</th>
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<tbody>
<tr>
<td><strong>All Patients</strong></td>
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<tr>
<td>------------------</td>
</tr>
<tr>
<td>Group I</td>
</tr>
<tr>
<td>Group II</td>
</tr>
<tr>
<td>Non-PV triggers</td>
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<tr>
<td>NPAF</td>
</tr>
</tbody>
</table>

The analysis was adjusted for age, sex, comorbidities, LA size >4, and non-PV triggers; group III is used as reference group for group I and group II. ATa = atrial tachyarrhythmia; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.
uncontrolled hypertension, found that age and LV mass were the sole predictor of new AF onset. These results may imply that, because of increased peripheral vascular resistances, patients with uncontrolled hypertension can develop elevated end-diastolic LV pressure and LV hypertrophy. Subsequently, increased LA pressure may cause atrial stretch and dilation, which may favor the development of AF (22). As a matter of fact, in our study, patients with uncontrolled hypertension presented higher LA size.

Tanabe et al. (23) compared PAF patients with hypertension or not and, at 2 years follow-up, found a statistical difference in terms of AF freedom (83% vs. 23%) and of LA diameter (39 ± 4 mm vs. 43 ± 7 mm) between patients with good and poor BP control, respectively. The authors suggested that LA overload related to poor BP control can affect AF burden.

Induced chronic hypertension in animal studies is associated with significant electrical and structural atrial remodeling (24). In an ovine model of induced hypertension, Lau et al. (25) showed an increase in slow atrial conduction and interstitial atrial fibrosis. These changes progressively increased the duration of induced AF episodes. Moreover, in a human study by Wang et al. (26), hypertension significantly increased the size of the LA scar and low-voltage zones in both paroxysmal and persistent AF patients. Our data demonstrated higher prevalence of moderate-or-severe scar in patients with hypertension, especially when it is uncontrolled. This may imply that patients with hypertension have more diseased atria, especially when hypertension is uncontrolled.

**AF ABLATION AND HYPERTENSION.** In the context of AF ablation, hypertension represents an important pre-procedural predictor of recurrence. Berruezo et al. (11) showed how hypertension and LA diameter are the main predictors of AF recurrence after PVAI and suggested the potential role of poor control of hypertension. These data were also confirmed by Letsas et al. (27), who found a cutoff value of LA diameter (≥43 mm) for AF recurrence.

Although the role of renal denervation for BP control in patients with drug-resistant hypertension is still controversial (28), some authors have tried to combine AF ablation with this technique.

Recently, Pokushalov et al. (29) randomized patients with drug-resistant hypertension, despite treatment with ≥3 antihypertensive drugs, to PVAI alone and PVAI plus renal artery denervation. At 1-year follow-up, they observed a statistical difference in terms of AF recurrence between patients treated with PVAI and renal artery denervation versus the PVAI-alone group (69% vs. 29% of AF freedom, respectively). Patients in both groups had paroxysmal or persistent AF with a large LA diameter of about 50 mm, associated with higher recurrence rate, especially if PVAI alone was performed (30,31).

A meta-analysis evaluating renal denervation associated with PVAI in different settings of patients found that this technique has higher efficacy among patients with persistent AF and/or severe resistant hypertension (32).

These data might support the concept that the ablation of afferent renal nervous input, decreasing the central sympathetic output (33), could attenuate autonomic triggers of AF (34). Furthermore, the authors reported a 10% reduction of LV mass in those patients who underwent renal artery denervation (35). The intriguing relationship between AF and hypertension could be associated with the sympathetic nerve activity, which could be linked to both AF occurrence (36) and high systolic BP values (37).

**UNCONTROLLED HYPERTENSION.** Uncontrolled hypertension is often related to myocardial infarction (38) and stroke (39) and could represent an adjunctive risk factor for AF maintenance. Our data show that patients with uncontrolled hypertension have increased atrial size, higher prevalence of non-PV triggers, and moderate/severe atrial scar. All these features could result in a more advanced atrial disease and progression of AF from paroxysmal to nonparoxysmal (40). In our analysis, the presence of uncontrolled hypertension, non-PV triggers, and NPAF were the strongest predictors of recurrence at multivariable analysis. Furthermore, after stratifying for AF type, uncontrolled hypertension, when associated with NPAF, confers a high risk of recurrence (HR: 2.59, 95% CI: 1.31 to 5.13, p = 0.006). This finding could imply that the progression of AF could also be related to a poor control of BP.

In patients with uncontrolled hypertension, in addition to the PVs, non-PV triggers became a necessary target for a successful ablation. Indeed, it

### TABLE 5  Procedural Complications

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 160)</th>
<th>Group II (n = 192)</th>
<th>Group III (n = 179)</th>
<th>Overall p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic complication (TIA or stroke)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0.74</td>
</tr>
<tr>
<td>Groin hematoma</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Values are n.

TIA = transient ischemic attack.
appears that the prevalence of these triggers increases substantially with the progression of the atrial disease (41).

When PVAI alone is performed in patients with uncontrolled hypertension, the rate of recurrence increased to 62.7%. On the other hand, when additional non-PV trigger ablation was performed, recurrence was 30.2%. It is possible that elimination of these triggers increases the success rate of the procedure in terms of AF-free survival, and restoring sinus rhythm could also have an impact on the progression of the atrial disease (42).

When additional non-PV trigger ablation was performed, in all groups, the overall success rate of the procedure was higher when it was not performed. Furthermore, comparing patients with uncontrolled hypertension who received additional non-PV trigger ablation with patients with controlled hypertension, no differences in terms of AF recurrence were found. This ablation strategy requires longer procedure time and a higher number of RF applications but significantly reduces the rate of AF recurrence. However, pharmacological control of BP could reduce post-ablation recurrences, and strict monitoring of BP during the post-procedural follow-up is crucial. Gaining pharmacological control of BP could reduce recurrences. On the other hand, also restoring sinus rhythm through RF ablation or cardioversion may result in BP reduction (43,44). Further studies are needed on this topic.

Uncontrolled hypertension has to be considered as a pre-procedural AF recurrence risk factor and, together with the type of AF, could predict the progression of atrial disease. Non-PV triggers, recognized during the procedure, represent a target of ablation, and successful elimination of these triggers confers a higher rate of AF freedom.

**STUDY LIMITATIONS.** This is not a randomized study; the ablation strategy was decided by the operator, so no conclusion can be drawn about the real benefit of additional non-PV trigger ablation.

All the procedures were performed under general anesthesia, which did not allow recognition of all non-PV triggers; however, because patients in both groups received the same anesthesia protocol, it may warrant uniformity of data.

LA dimension was evaluated only through measurement of the anterior-posterior diameter; no data were collected on LA volume and/or area.

Because patients were referred to our institutions only for EP evaluation, no information is available about hypertension management at long-term follow-up.

**CONCLUSIONS**

Controlled hypertension does not affect the AF ablation outcome when compared with patients without hypertension. On the contrary, uncontrolled hypertension confers higher AF recurrence risk and requires an extensive ablation.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** Hypertension represents one of the main predictors of atrial fibrillation ablation procedural failure. In this study, patients with pharmacologically uncontrolled hypertension had a higher recurrence rate when compared with patients without hypertension or with hypertension controlled by medications, if the ablation procedure was limited to pulmonary vein isolation alone. However, when these patients underwent ablation of all non-pulmonary vein triggers, they had a similar recurrence rate as patients without hypertension.

**TRANSLATIONAL OUTLOOK:** Randomized controlled trials are needed to confirm the clinical relevance of our findings and the role of ablation in the setting of hypertension.

**REFERENCES**


**KEY WORDS** atrial fibrillation, catheter ablation, hypertension, non-PV triggers, pulmonary vein isolation, uncontrolled hypertension