



Original Article

# Effect of Perindopril on Atrial Fibrillation Recurrence and Burden: Results of the Canadian Trial of Atrial Fibrillation (CTAF)-2

Lena Rivard, MD, MSc,<sup>a,†</sup> Michelle Samuel, MPH, PhD,<sup>a,†</sup> Annik Fortier, MSc,<sup>b</sup> Marie-Claude Guertin, PhD,<sup>b</sup> Paul Khairy, MD, PhD,<sup>a</sup> Denis Roy, MD,<sup>a</sup> Mario Talajic, MD,<sup>a</sup> and Jean-Claude Tardif, MD<sup>a</sup>

<sup>a</sup> Research Centre, Montreal Heart Institute, Université de Montréal, Montreal, Quebec, Canada

<sup>b</sup> Montreal Health Innovations Coordinating Center, Montreal Heart Institute, Montreal, Quebec, Canada

## ABSTRACT

**Background:** Hypertension is a risk factor for the development and exacerbation of atrial fibrillation (AF). Angiotensin-converting enzyme inhibitors are a standard-of-care treatment option for patients with hypertension; however, there is conflicting evidence about their effects on AF recurrence. Therefore, our objective was to assess the efficacy of perindopril, compared with placebo, to reduce AF recurrence in patients with hypertension and AF.

**Methods:** In a multicenter, double-blind, placebo-controlled trial, patients with hypertension and symptomatic AF were randomly assigned (1:1) to perindopril or placebo based on a stratification factor of antiarrhythmic drug use. Patients with terminated AF were followed up from 30 days after randomization to 7 to 13 months. The primary endpoint was AF recurrence. Secondary endpoints included AF hospitalization, cardioversion, and blood pressure control. Recurrent events, AF burden, and safety endpoints were also investigated.

**Results:** A total of 315 patients were randomly assigned, and 301 patients were included in the modified intent-to-treat analysis (155 vs

## RÉSUMÉ

**Introduction :** L'hypertension est un facteur de risque de l'apparition et de l'exacerbation de la fibrillation auriculaire (FA). Les inhibiteurs de l'enzyme de conversion de l'angiotensine représentent une option de traitement qui répond à la norme de soins à prescrire aux patients hypertendus. Toutefois, les données probantes concernant leurs répercussions sur la récurrence de la FA sont contradictoires. Par conséquent, notre objectif était de comparer l'efficacité du péridopril au placebo dans la réduction de la récurrence de la FA chez les patients hypertendus atteints de FA.

**Méthodes :** Dans un essai multicentrique en double aveugle contre placebo, nous avons réparti de façon aléatoire (1:1) les patients hypertendus atteints de FA symptomatique au péridopril ou au placebo en fonction d'un facteur de stratification de l'utilisation de médicaments antiarythmiques. Nous avons suivi les patients, dont la FA a cessé, du 30<sup>e</sup> jour après la répartition aléatoire jusqu'au 7<sup>e</sup> au 13<sup>e</sup> mois. Le critère d'évaluation principal était la récurrence de la FA. Les critères secondaires étaient les suivants : l'hospitalisation en raison de la FA,

Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with an increased risk of stroke, death, and heart failure.<sup>1,2</sup> Hypertension is a strong risk factor for the development and exacerbation of AF. Both diseases frequently coexist with almost two-thirds of AF patients having comorbid hypertension.<sup>3</sup> Therefore, effective primary and secondary prevention of AF in hypertensive patients is warranted.

Angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-II receptor blockers (ARB) are effective in the

treatment of hypertension and reduce morbidity and mortality in patients with heart failure or left ventricular systolic dysfunction after myocardial infarction.<sup>4,5</sup> Several meta-analyses of randomized controlled trials (RCTs) reported that both ACEis and ARBs appear to be effective in the prevention of AF in hypertensive patients with a reduction up to 54%.<sup>6-11</sup> Furthermore, 3 large population-level studies with long-term follow-up suggested a beneficial effect of ACEis or ARBs over diuretics and  $\beta$ -blockers on the occurrence of overt AF.<sup>12-14</sup> However, large RCTs reported conflicting results on the efficacy on primary and secondary prevention of AF in hypertensive patients. In the **Losartan Intervention for End Point Reduction in Hypertension (LIFE)** study,<sup>15</sup> losartan reduced the risk of new-onset AF and stroke compared with atenolol despite similar blood pressure (BP) control in hypertensive patients with left ventricular hypertrophy. Likewise, the **Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)** trial showed a significant reduction in the occurrence of new-onset AF with valsartan compared with amlodipine

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**Ethics Statement:** The CTAF-2 trial was approved by the institutional review board at all participating centers. The research reported in the present manuscript adhered to all relevant ethical guidelines.

<sup>†</sup> L. Rivard and M. Samuel contributed equally as co-first authors.

Corresponding author: Dr Jean-Claude Tardif, Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H1T 1C8, Canada. Tel.: 514 376-3330; Fax: 514 376-1355.

E-mail: [jean-claude.tardif@icm-mhi.org](mailto:jean-claude.tardif@icm-mhi.org)

See page 1106 for disclosure information.

146 patients in the perindopril and placebo groups, respectively). The mean follow-up was  $336 \pm 70$  days, and 91.1% of patients were compliant to the treatment medication throughout the study. After adjustment for baseline antiarrhythmic drugs, there was no statistically significant difference in the hazards of AF recurrence (hazard ratio, 1.22; 95% confidence interval, 0.92-1.61), with similar blood pressure. The incidence of secondary endpoints and adverse events also did not differ between treatment arms.

**Conclusions:** Perindopril does not reduce recurrence or the number of AF episodes in patients with hypertension and AF.

treatment.<sup>16</sup> In contrast, the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE I)<sup>17</sup> and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico-Atrial Fibrillation (GISSI-AF) trials failed to show any benefit on AF prevention.<sup>18</sup> Results have also been conflicting in secondary prevention of AF. In hypertensive patients with paroxysmal AF, Du et al<sup>19</sup> reported similar AF recurrence rates in the nifedipine and telmisartan groups; whereas, Fogari et al<sup>20</sup> found that valsartan and ramipril were more effective than amlodipine despite similar BP lowering.

The objective of this RCT was to assess the efficacy of the ACEi perindopril compared with placebo to reduce AF recurrence (assessed by transtelephonic electrocardiogram [ECG] monitoring [TTM]), cardioversion, AF hospitalizations, and AF burden in patients with hypertension and AF.

## Methods

### Trial design and oversight

In a prospective, multicenter, parallel-arm, placebo-controlled, double-blind, phase III, investigator-initiated trial, subjects were randomly divided in a 1:1 ratio, with a stratification factor for baseline antiarrhythmic drug (AAD) use, to receive either perindopril, 8 mg once daily, or placebo. In addition, patients received standard antihypertensive treatment according to guidelines.<sup>21</sup> The trial procedures have been previously published.<sup>22</sup> In summary, once patients were randomly assigned, each subject was given an initial dose of either 4 mg perindopril or placebo daily (based on randomization allocation). At 2 weeks, BP control, tolerability to study medications, and adverse events (AE) were evaluated. The dose of study medication was increased to 8 mg daily for the duration of the study for subjects without a nontolerable AE, without symptomatic orthostatic hypotension, and not deemed at risk of complications with a dose increase. Subjects with persistent AF were permitted to undergo electrical or

la cardioversion et la maîtrise de la pression artérielle. Nous avons aussi examiné les critères suivants : événements récurrents, fardeau de la FA et innocuité.

**Résultats :** Parmi les 315 patients répartis de façon aléatoire, nous avons sélectionné 301 patients pour l'analyse en intention de traiter modifiée (155 vs 146 patients, et ce respectivement, dans le groupe du péridopril et le groupe du placebo). Le suivi moyen a été de  $336 \pm 70$  jours, et 91,1 % de patients ont suivi fidèlement le traitement médicamenteux durant toute la durée de l'étude. Après l'ajustement initial des médicaments antiarythmiques, il n'y a eu aucune différence significative sur le plan statistique dans les risques de récurrence de la FA (ratio d'incidence approché 1,22 [intervalle de confiance à 95 %, 0,92-1,61]) en présence d'une pression artérielle similaire. La fréquence des critères secondaires et des événements indésirables n'a également pas différé entre les bras de traitement.

**Conclusions :** Le péridopril ne contribue pas à la réduction de la récurrence ou du nombre d'épisodes de FA chez les patients hypertendus atteints de FA.

pharmacologic cardioversion within the first 30 days after randomization. Subjects were followed up for 7 to 13 months and had clinical evaluations at 15 days, 30 days, and 4, 7, and 13 months after the date of randomization.

The trial protocol was designed by the steering committee and approved by the institutional review boards of all 40 participating centers ([Supplemental Appendix S1](#)). The trial was sponsored by Servier Canada Inc. Trial management, coordination, and all support activities (including statistical analyses) were conducted by the Montreal Health Innovations Coordinating Center. An independent data and safety monitoring board oversaw the trial and monitored AEs. The trial medications (perindopril and placebo) were supplied by the sponsor to the Montreal Health Innovations Coordinating Center for study distribution. The sponsor was not involved in daily study activities, data collection, or analyses.

### Trial population

Eligible patients were adults with hypertension (sitting systolic BP  $\leq 160$  mm Hg and diastolic BP  $\leq 100$  mm Hg at baseline visit) and electrocardiogram (ECG)-documented AF with at least 1 episode of symptomatic paroxysmal or persistent AF of  $\geq 10$  minutes within the last 6 months. Exclusion criteria included: (1) left ventricular systolic dysfunction (ejection fraction  $\leq 45\%$ ), (2) myocardial infarction within a month prior, (3) cardiac or thoracic surgery within the last 3 months or planned, (4) chronic AF, (5) AF secondary to a reversible condition, (6) any medical condition other than hypertension requiring an ACEi or ARB, (7) renal insufficiency, (8) bilateral renal artery stenosis, (9) recent serum potassium level of  $\geq 5$  mmol/L, (10) liver disease, (11) severely uncontrolled hypertension, (12) impossibility to discontinue lithium or potassium supplement, (13) history of angioedema related to previous treatment with ACEis, and (14) contraindication to perindopril. Detailed inclusion and exclusion criteria are listed in [Supplemental Appendix S2](#). Written informed consent was acquired from all eligible patients before enrollment.

## Endpoints

A blanking period of 30 days postrandomization was applied to (1) exclude very early AF recurrence (not related to trial medication); (2) monitor tolerability, BP control, and AEs potentially related to the trial medication; and (3) perform electrical or pharmacologic cardioversion in persistent AF patients. Day 31, from the date of randomization, was taken to represent the start of follow-up, and only endpoints captured on and after that date were included in the analyses.

The primary efficacy endpoint was defined as the time to first ECG-documented AF recurrence during follow-up (ie, AF documented on 12-lead ECG, TTM, or 24-hour Holter monitoring). Time 0 (start of follow-up) was day 31 after randomization. Subjects in persistent AF at the end of the 30-day period after randomization were considered to have had AF recurrence on day 1 of follow-up. Secondary efficacy endpoints included AF recurrence within the first 6 months of follow-up, successful cardioversion, AF hospitalization, and BP control (sitting systolic BP < 140 mm Hg and diastolic BP < 90 mm Hg) or reduction (sitting systolic BP  $\geq$  20 mm Hg or sitting diastolic BP  $\geq$  10 mm Hg). The numbers of documented relapses of AF and AF hospitalizations during follow-up were also captured. In addition, AF burden was estimated from TTM. Only patients with at least 2 TTMs were included in this analysis. AF burden per patient was calculated as the number of TTMs with AF reported divided by the total number of TTMs. AF burden was also calculated with the interval approach.<sup>23</sup> Follow-up was divided into allotments of time (days), based on the date of consecutive TTM measures. Person-time (days) was classified as in sinus rhythm or AF based on the consecutive TTM ECGs. When the rhythm differed between 2 consecutive TTMs, 50% of the person-time was classified as in AF, and 50% of the person-time was classified as in sinus rhythm. Thus, AF burden was calculated as the proportion of person-time in AF over the total person-time in the study.

Safety outcomes, including AEs, were captured from laboratory parameters, transtelephonic ECG monitoring, standard 12-lead ECG parameters, BP monitoring, and physical examinations.

## Follow-up

Patients who remained in the study after the 30-day blanking period, were followed up until the end of study (12 months after the blanking period) or withdrawal from study, whichever was first. Follow-up visits were specified at 3, 6, and 12 months postbaseline to assess outcomes and changes in BP and medications. TTMs captured the outcome of AF recurrence. Patients were advised to send weekly TTMs and to report symptoms (if any), regardless of symptoms. Class I and class III AADs and ablative therapies were strongly discouraged during the course of the study

## Statistical analysis

Sample size calculations assumed that 50% of subjects in the control arm would have AF recurrence within 6 months of follow-up (day 31 to 7 months post randomization). For a clinically meaningful absolute reduction in AF recurrence of 15% in the treatment arm compared with the control arm, a

sample size of 130 patients per arm was calculated to be necessary with 2-sided  $\alpha = 0.05$ , 80% power, and a log-rank test for the comparison of 2 survival curves using the Kaplan-Meier method. To account for potential loss to follow-up (assuming a rate of 18%), the final sample size was increased to 320 subjects.

The primary efficacy analysis was performed on a modified ITT population and was replicated in the ITT population. The latter population consisted of all randomly assigned patients, whereas the modified ITT population only included subjects from ITT population who had a visit at day 30. The primary endpoint, time to first AF recurrence, was analyzed using a log-rank test stratified for baseline AAD use as well as a Cox proportional hazards model adjusted for baseline AAD use. Kaplan-Meier curves were also constructed.

Occurrence of AF within the first 6 months of follow-up, as well as successful cardioversion, hospitalization, or BP control at 12 months of follow-up were analyzed using a Mantel-Haenszel test stratified for baseline AAD use. Median and interquartile range (IQR) for AF burden was compared between treatment arms with the Mann-Whitney-Wilcoxon test. A negative binomial model was used to investigate the number of documented relapses of AF. Additional analyses taking into account missing data and subgroup analyses, including patients with persistent AF, paroxysmal AF, and impregnated renin-angiotensin-aldosterone system (RAAS), were also conducted.

AEs were reported using frequency (percentage), and group comparisons were done using  $\chi^2$  tests. All analyses do not account for multiple comparisons and were completed using SAS 9.3 or higher (SAS Institute Inc., Cary, NC).

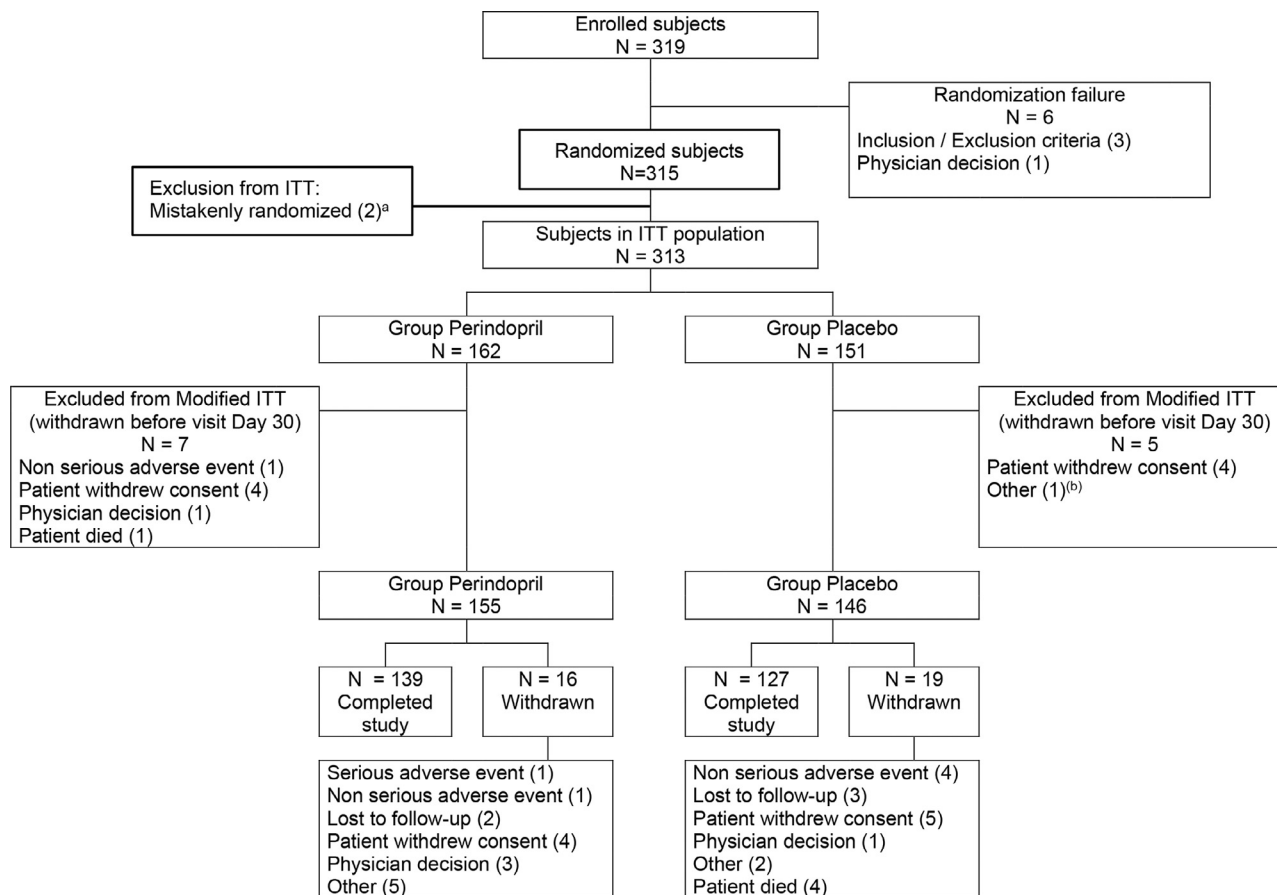
## Results

### Trial subjects

A total of 315 subjects were randomly assigned; however, 14 subjects were excluded from the modified ITT population (N = 301; 155 vs 146 subjects randomly assigned to perindopril and placebo, respectively). Reasons for discontinuation from the study were nonserious adverse event (n = 1), withdrawal of consent (n = 8), physician decision (n = 1), death (n = 1), and missing data (n = 1). Two subjects randomized by error were also excluded. Approximately 89.7% of perindopril and 87.0% of placebo subjects completed the trial follow-up of 6 to 12 months (mean follow-up,  $335 \pm 71$  days vs  $337 \pm 68$  days, perindopril vs placebo arm, respectively). Trial enrollment began in September 2006, and the last patient was enrolled in September 2012; the last trial visit was June 2013. The trial flow and disposition of subjects are further detailed in [Figure 1](#).

Overall, patient characteristics were similar between treatment arms in the modified ITT population ([Table 1](#)). Trial subjects were a mean age of  $66.4 \pm 9.7$  years, 58.5% were men, and most subjects had paroxysmal AF (81.7%). In addition, most subjects were prescribed oral anticoagulation (77.4%) and AADs (70.4%) in the year before enrollment.

Overall compliance to the trial medication regimen was 91.1%. Subjects randomly assigned to perindopril were exposed to the study medication for a shorter duration



**Figure 1.** Subjects flow chart. <sup>a</sup> Patients were on valsartan, which should have excluded them from the study. <sup>b</sup> This subject did not withdraw before day 30 but had no day 30 visit and had very few data collected and was therefore excluded from the modified intent-to-treat (ITT) population.

(317 ± 133 days) compared with those assigned to placebo (343 ± 109 days); however, the difference was not statistically significant ( $P = 0.0632$ ). Reasons for discontinuation of the study included serious adverse events (1 subject), AEs (5 subjects), withdrawal of consent (9 subjects), lost to follow-up (5 subjects), physician decision (4 subjects), death (4 subjects), and other (7 subjects).

Approximately 59.3% ( $n = 179$ ) of subjects submitted ≥ 70% of the requisite weekly TTM transmissions for the trial. Compliance for weekly TTM transmissions did not differ between treatment arms (≥ 70% of weekly transmissions were received from 59.1% of the perindopril arm and 60.3% of the placebo arm).

### Clinical efficacy endpoints

Over a mean follow-up time of 336 ± 70 days, 107 (69.0%) perindopril subjects and 89 (61.0%) placebo subjects had an AF recurrence (Table 2). Twenty-two (14.2%) perindopril subjects and 17 (11.5%) placebo subjects were in AF at the beginning of follow-up (day 31). After adjustment for baseline AAD use, there was no statistically significant difference in the hazard ratio (HR) of AF recurrence (HR, 1.22; 95% confidence interval [CI], 0.92-1.61) between treatment arms, which is further illustrated by the Kaplan-Meier curves

(log-rank  $P = 0.19$ ; Figure 2). Further, there was no statistically significant difference in AF recurrences within 6 months of follow-up or in AF burden between patients randomly assigned to perindopril or placebo ( $P > 0.05$  for all).

Sixteen (10.3%) perindopril subjects had a cardioversion compared with 12 (8.2%) placebo subjects ( $P = 0.54$ ). AF hospitalizations occurred in 12 (7.7%) perindopril subjects and 11 (7.5%) placebo subjects ( $P = 0.97$ ). In addition, there was no statistically significant difference in BP reduction or control between treatment arms (Table 2). Twelve months after randomization, the median systolic BP was 133 (IQR, 121-140) mm Hg in the perindopril arm and 135 (IQR, 127-146) mm Hg in the placebo arm (3.8% of patients were on concomitant antihypertensive therapy during follow-up).

Similar to the evaluations of time-to-first clinical event, there was also no statistically significant difference for multiple AF recurrences, cardioversions, and AF hospitalizations (recurrent events) between subjects on perindopril compared with those on placebo (Table 3). In addition, all sensitivity and subgroup analyses performed on the primary endpoint showed no statistically significant difference between treatment arms ( $P > 0.05$  for all; results presented in Supplemental Appendix S3). In subgroup analyses by type of AF, no statistically significant difference was detected between

**Table 1. Baseline characteristics (modified intent-to-treat population)**

Characteristics	Perindopril (N = 155)	Placebo (N = 146)	P value
Age (mean ± SD), y	66.6 ± 9.6	66.2 ± 9.9	0.73
Female, n (%)	60 (38.7)	65 (44.5)	0.31
Type of AF, n (%)			0.69
Paroxysmal	128 (82.6)	118 (80.8)	
Persistent	27 (17.4)	28 (19.2)	
Dyslipidemia, n (%)	96 (61.9)	77 (52.7)	0.11
Diabetes, n (%)	20 (12.9)	19 (13.0)	0.98
Prior myocardial infarction, n (%)	14 (9.0)	9 (6.2)	0.35
Prior stroke or TIA, n (%)	10 (6.5)	8 (5.5)	0.72
Chronic renal insufficiency, n (%)	1 (0.6)	2 (1.4)	0.53
Congestive heart failure, n (%)	6 (3.9)	5 (3.4)	0.84
LVEF (mean ± SD), %	62.5 ± 8.6	62.7 ± 7.7	0.82
Cardiac implantable devices, n (%)			
Pacemaker	8 (5.3)	6 (4.1)	0.64
Implantable cardioverter defibrillator	0 (0.0)	2 (1.4)	0.14
Prior AF catheter ablation, n (%)	5 (3.2)	4 (2.7)	0.80
Medications			
Use of antiarrhythmic drugs for the last year, n (%)	108 (69.7)	104 (71.2)	0.77
Amiodarone	18 (11.6)	7 (4.8)	0.03
Sotalol	27 (17.4)	30 (20.5)	0.49
Propafenone	13 (8.4)	15 (10.3)	0.57
Flecainide	13 (8.4)	8 (5.5)	0.32
Digoxin	14 (9.0)	9 (6.2)	0.34
Verapamil or diltiazem	22 (14.2)	13 (8.9)	0.15
Other	7 (4.5)	6 (4.1)	0.86
Antihypertensive medication, n (%)			
β-blockers (other than Sotalol)	57 (36.8)	56 (38.4)	0.78
Diuretics	49 (31.6)	68 (46.6)	0.008
Oral anticoagulation, n (%)	121 (78.1)	112 (76.7)	0.77

AF, atrial fibrillation; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.

treatment arms for the incidence of the primary endpoint in patients with paroxysmal AF (n = 246 patients; HR, 1.16; 95% CI, 0.85-1.58) and persistent AF (n = 28 patients; HR, 1.51; 95% CI 0.76-3.00) (results presented in [Supplemental Appendix S3](#)).

**Table 2. Major clinical endpoints (modified intent-to-treat population)**

Endpoint	Perindopril (N = 155)	Placebo (N = 146)	P value
<b>Primary endpoint*</b>			
First occurrence of AF, n (%)	107 (69.0)	89 (61.0)	HR, 1.22 (95% CI, 0.92-1.61) 0.17
<b>Secondary endpoints<sup>†</sup></b>			
AF recurrence within 6 months, n (%)	96 (64.4)	76 (53.1)	0.05
Successful cardioversion, n (%)	16 (10.3)	12 (8.2)	0.54
Hospitalization for AF, n (%)	12 (7.7)	11 (7.5)	0.97
BP control, n (%) <sup>‡</sup>			
Sitting SBP < 140 mm Hg and DBP < 90 mm Hg	99 (68.3)	79 (59.0)	0.12
Reduction in sitting SBP ≥ 20 mm Hg	21 (14.5)	13 (9.7)	0.24
Reduction in sitting DBP ≥ 10 mm Hg	23 (15.9)	31 (23.1)	0.11
<b>Tertiary endpoint<sup>§</sup></b>			
AF burden measure by percent TTMs, median (IQR)	9.1 (0.0-30.7)	8.4 (0.0-29.4)	0.36
AF burden measured by interval of time between TTMs, median (IQR)	7.6 (0.0-30.1)	6.0 (0.0-27.7)	0.28

AF, atrial fibrillation; BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; IQR, interquartile range; SBP, systolic blood pressure; TTM, transtelephonic electrocardiogram monitoring.

\*Cox model adjusted for baseline antiarrhythmic medication use was conducted for the primary endpoint only.

<sup>†</sup>Mantel-Haenszel test stratified for baseline antiarrhythmic medication use was conducted for all secondary outcomes.

<sup>‡</sup>BP measurements compared between randomization and end of follow-up.

<sup>§</sup>From a total of 147 patients in the perindopril arm and 142 patients in the placebo arm who had at least 2 TTMs. A Wilcoxon rank sum test was used to compare medians between treatment arms.

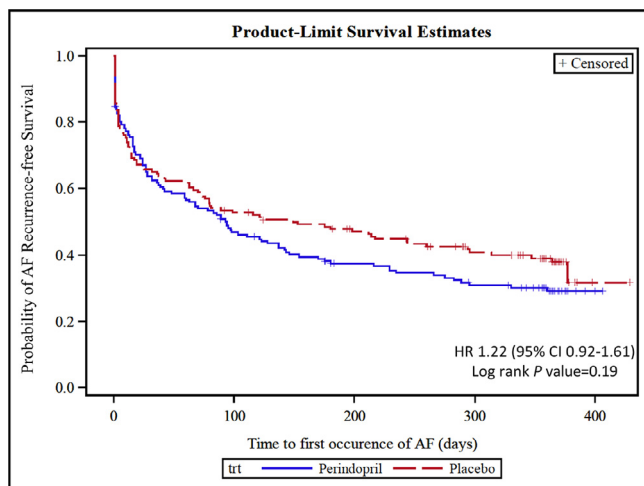
## Adverse events

The incidence of treatment-emergent AEs was comparable in perindopril (116 events, 70.3%) and placebo (98 events, 65.3%) subjects ( $P = 0.35$ ; [Table 4](#)).

## Discussion

The results of this multicenter RCT showed that perindopril in addition to AAD therapy did not prevent AF recurrence, AF hospitalizations, or cardioversions when compared with placebo in patients with hypertension and documented AF during a mean of 11.2 months of follow-up with similar BP lowering. The incidence of AF recurrence also did not differ between treatment arms according to whether patients had paroxysmal and persistent AF. Furthermore, secondary and tertiary efficacy endpoints that include AF burden, AF recurrence within the first 6 months of follow-up, successful cardioversion, and AF hospitalization were not different between groups.

Although there were previously limited data on the effects of ACEi against AF in the specific population of hypertensive patients with documented AF, the results with ARB have previously been conflicting. In a multicenter RCT, Galzerano et al<sup>24</sup> assessed the efficacy of an antihypertensive therapeutic dose of telmisartan (80 mg once daily) compared with that of the β-blocker carvedilol (25 mg once daily) for the prevention of AF recurrence in 132 hypertensive patients with a recent history of AF. During the 12-month study period, telmisartan was significantly more effective than carvedilol in preventing recurrent AF episodes (14.3% vs 37.1%;  $P < 0.003$ ;  $\chi^2$  test).<sup>24</sup> Telmisartan was also more effective than amlodipine in preventing AF recurrences in 378 mild hypertensive outpatients with a history of paroxysmal AF despite a similar BP reduction.<sup>25</sup> Those results were confirmed by Pan et al<sup>10</sup> in a meta-analysis that found superiority of telmisartan compared with other antihypertensive drugs on the risk of AF recurrence in hypertensive patients with paroxysmal AF. One limitation of those studies is the lack of a placebo group. Of note, most



**Figure 2.** Kaplan-Meier curve for first atrial fibrillation (AF) recurrence (modified intent-to-treat population). Time 0 corresponds to day 31, which is the start of follow-up. Kaplan-Meier curves are unadjusted for concurrent antiarrhythmic drug use.

of the RCTs in hypertensive patients had a short follow-up (1 to 2 years) and only used ECG-documented AF and not TTM as a primary endpoint. Our results are in line with those of the **Angiotensin II Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF)** RCT in which 435 patients with documented AF without structural heart disease were randomly

**Table 3. Recurrent events**

Endpoint	Perindopril (N = 155)	Placebo (N = 146)	RR (95% CI)
<b>AF recurrence</b>			
Number of AF events per patient, n (%)			
0	48 (31.0)	57 (39.0)	
1	21 (13.5)	11 (7.5)	
2	11 (7.1)	10 (6.8)	
3	7 (4.5)	5 (3.4)	
4	8 (5.2)	4 (2.7)	
5-10	22 (14.2)	24 (16.4)	
≥ 10	38 (24.5)	35 (24.0)	
Total number of AF events	1356	1143	
Total follow-up months	1701.7	1615.1	
Rate of primary endpoint events per 100 patient-months	79.7	70.8	
Negative binomial model			1.17 (0.78-1.75)
<b>AF hospitalizations</b>			
Number of AF hospitalizations per patient, n (%)			
0	143 (92.3)	135 (92.5)	
1	10 (6.5)	8 (5.5)	
2	2 (1.3)	3 (2.1)	
Total number of AF hospitalizations events	14	14	
Total follow-up months	1701.7	1615.1	
Rate of primary endpoint events per 100 patient-months	0.82	0.87	
Negative binomial model			0.91 (0.39-2.13)

Recurrent events presented as the median number of events and inter-quartile range. Negative binomial regression was used to compare groups. AF, atrial fibrillation; CI, confidence interval; RR, relative risk.

**Table 4. Adverse events (safety population)**

Events	Perindopril (N = 165)	Placebo (N = 150)	P value
TEAEs, n (%)*	116 (70.3)	98 (65.3)	0.35
Related TEAEs <sup>†</sup>	39 (23.6)	31 (20.7)	0.53
Gastrointestinal event	4 (2.4)	8 (5.3)	0.18
Vascular disorders	5 (3.0)	3 (2.0)	0.73 <sup>‡</sup>
Dizziness	5 (3.0)	9 (6.0)	0.20
Headache	3 (1.8)	5 (3.3)	0.49 <sup>‡</sup>
Cough	16 (9.7)	6 (4.0)	0.05
Related TEAEs <sup>†</sup>	2 (1.2)	1 (0.7)	1.00 <sup>‡</sup>
Gastrointestinal event <sup>§</sup>	1 (0.6)	0 (0.0)	1.00 <sup>‡</sup>
Increased blood pressure	1 (0.6)	0 (0.0)	1.00 <sup>‡</sup>
Transient ischemic attack	0 (0.0)	1 (0.7)	0.48 <sup>‡</sup>

Chi-squared tests were performed to compare the incidence of adverse events between treatment arms.

AE, adverse event; TEAE, treatment-emergent adverse event.

An AE is considered treatment emergent if it occurs after the first dose of study medication is dispensed (ie, if AE onset date on or after date medication dispensed to patient).

<sup>†</sup>A related TEAE or serious AE is any TEAE that is possibly, probably, or definitely related to study drug as recorded in the case report form. All serious AEs and only AEs with an incidence ≥ 2% were listed in Table 3.

<sup>‡</sup>Because of the low number of AEs, the Fisher Exact test was performed instead of the  $\chi^2$  test. The safety population includes subjects who were still on the study medication at day 31 (start of follow-up).

<sup>§</sup>One (0.6%) patient in the perindopril arm had a serious AE of acute pancreatitis.

assigned to olmesartan or placebo.<sup>26</sup> AF burden (assessed by TTM) was the primary endpoint, and nearly half of the population suffered from arterial hypertension. After 1-year follow-up, olmesartan did not reduce AF burden compared with placebo. Identical results were found in a small RCT comparing nifedipine with telmisartan in the absence of AADs in 149 hypertensive patients.<sup>19</sup> After 2 years of follow-up, the incidence of AF recurrence was identical in both arms. Likewise, in a retrospective analysis of the Canadian Trial of Atrial Fibrillation (CTAF) study, RAAS blockade did not provide additional benefit to AAD treatment against AF recurrence.<sup>27</sup> However, the combination of valsartan/amlodipine was more efficient than that of atenolol/amlodipine in preventing AF recurrence in addition to AADs in an RCT performed in diabetic hypertensive patients.<sup>20</sup>

It is unknown if a longer treatment duration and/or RAAS blockade in primary prevention may be more effective to reduce AF. Indeed, in 3 large cohorts with long-term follow-up, RAAS blockade was efficient in primary prevention of AF.<sup>12-14</sup> A Danish study of 725,680 participants with treated hypertension and no additional AF risk factors found that ACEi and ARB monotherapy decreased the risk of AF development after a follow-up of more than 6.5 years when compared with  $\beta$ -blockers and diuretics.<sup>12</sup> Hsieh et al<sup>13</sup> reported identical effects of ARB and ACEi on new-onset AF in hypertensive patients in the Taiwan National Health Insurance Research Database.<sup>13</sup> During an average of 7.7 years of follow-up, 6.5% of patients had AF (overall incidence of 8.4/1000 person-years). The incidence of new-onset AF was lower in both ARB (5.6/1000 person-years; adjusted HR, 0.51; 95% CI, 0.44-0.58) and ACEi users (6.2/1000 person-years; adjusted HR, 0.53; 95% CI, 0.47-0.59) compared with non-users (11.7/1000 person-years). Likewise, the results from the United Kingdom-based General Practice Research Database showed that long-term treatment with ACEis, ARBs, or

$\beta$ -blockers reduces the risk for AF compared with calcium-channel blockers in hypertensive patients.<sup>14</sup> Further, a sub-analysis of the LIFE study reported a lower AF risk with losartan when compared with atenolol, and the VALUE study found a lower risk of AF with valsartan compared with amlodipine.<sup>15,16</sup> In both trials, AF was<sup>28</sup> diagnosed based on yearly ECGs. Thus, the true incidence of AF may have been underestimated.

Activation of the RAAS system increases structural remodeling and is elevated in AF.<sup>29,30</sup> Hypothesized mechanisms for the suspected antiarrhythmic effects of ACEis and ARBs include inhibition of electrical and structural cardiac remodeling and neurohumoral activation, reduction of BP, and stabilization of electrolyte disturbances.<sup>31-36</sup> Once AF has developed and a certain amount of atrial fibrosis and remodeling is present, antihypertensive therapies may be less effective to prevent AF recurrence. As such, a difference in AF recurrence may not have resulted in this study because all subjects had AF.

ARB may cause greater favorable effects on atrial electrophysiologic properties, P-wave dispersion, and P-wave duration values than ACEi.<sup>37</sup> In hypertensive patients with left ventricular hypertrophy, losartan significantly decreased myocardial collagen content compared with atenolol despite a comparable decrease in arterial pressure.<sup>33</sup> Hypertension, sleep apnea, and obesity are associated with increased RAAS activation,<sup>38,39</sup> and multiple pathway interventions that include weight reduction, sleep apnea treatment, and pharmacologic medications may be the most effective strategy to reduce AF.<sup>40</sup>

### Limitations

The relatively short follow-up period in this study does not allow drawing conclusions on the effect of longer-term RAAS blockade. AF burden was assessed by TTM; thus, silent AF recurrences may have been underestimated. Although 40 centers participated in CTAF-2, the enrollment rate was low, signaling potential selection bias. Generalizability of the results should be interpreted within the context of recruitment that terminated in 2013. Clinical management has since changed in favor of a less-extensive use of antiarrhythmic drugs owing to a higher rate of AF ablation procedures. Likewise, the 2014 Canadian Cardiovascular Society guidelines recommended broadening anticoagulation indications to all AF patients older than 65 years (or with any risk factor for stroke, ie, Congestive Heart Failure, Hypertension, Age 65 years, Diabetes, Stroke/Transient Ischemic Attack [CHADS-65]).<sup>41</sup> Changes in concomitant medications, such as AADs, was not collected in the trial.

### Conclusion

In patients with hypertension and documented AF, perindopril did not prevent AF recurrences, AF hospitalizations, or cardioversions when compared with placebo.

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### Supplementary Material

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