Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) Trial

Andreas Goette, MD; Norbert Schön, MD; Paulus Kirchhof, MD; Günter Breithardt, MD; Thomas Fetsch, MD; Karl Georg Häusler, MD; Helmut U. Klein, MD; Gerhard Steinbeck, MD; Karl Wegscheider, PhD; Thomas Meinertz, MD

Background—Unlike antiarrhythmic drugs, the safety and beneficial effects of angiotensin II receptor blockade (ARB) in patients with structural heart disease is well established. The clinical efficacy of ARBs to prevent atrial fibrillation (AF) so far only has been shown in patients with structural heart disease. Here, we report the primary outcome of the Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial, which investigated the effect of olmesartan medoxomil compared with placebo on AF burden in patients with paroxysmal AF without structural heart disease.

Methods and Results—The ANTIPAF trial was a prospective, randomized, placebo-controlled, multicenter trial analyzing the AF burden (percentage of days with documented episodes of paroxysmal AF) during a 12-month follow-up as the primary study end point. Four hundred thirty patients with documented paroxysmal AF without structural heart disease were randomized to placebo or 40 mg olmesartan per day. Concomitant therapy with ARBs, angiotensin-converting enzyme inhibitors, and antiarrhythmic drugs was prohibited. Patients were followed using daily transtelphonic ECG (tele-ECG) recordings independent of symptoms. The intention-to-treat population of the trial encompassed 425 patients (placebo group, n=211; olmesartan group, n=214). A total of 87 818 tele-ECGs were analyzed in these patients during follow-up (placebo group, 44 888 ECGs; olmesartan group, 42 930 ECGs). Thus, a mean of 207 tele-ECGs were recorded per patient. The primary end point (AF burden) was not different between the 2 groups (P=0.770). Secondary outcome parameters, including quality of life, also were not different. In particular, time to first AF recurrence, time to persistent AF, and number of hospitalizations were not different between the 2 groups. The time to prescription of recovery medication (amiodarone) was the only parameter showing an intergroup difference, with earlier prescription of amiodarone in the placebo group (P=0.022).

Conclusions—One year of ARB therapy per se does not reduce the number of AF episodes in patients with documented paroxysmal AF without structural heart disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00098137.

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Key Words: angiotensin ■ atrial fibrillation ■ remodeling ■ olmesartan ■ telemedicine

Atrial fibrillation (AF) is the most common sustained arrhythmia and associates with relevant excess morbidity and mortality.1–3 So far, we are unable to prevent many of the severe complications associated with AF, despite antithrombotic therapy and “aggressive” management of concomitant heart disease.2–4 Specifically, the perceived benefit of rhythm control therapy by antiarrhythmic drugs appears to be offset by proarrhythmic side effects.2

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Pharmacological inhibition of the renin-angiotensin system improves survival in patients with structural heart disease and...
clearly is a safe intervention in most patients with AF.\textsuperscript{5,6} There is good experimental evidence that angiotensin II receptor blockade (ARB) therapy can prevent structural remodeling\textsuperscript{6–9} and occurrence of AF in patients with structural heart disease.\textsuperscript{5,10,11} Given the observation that AF induces atrial fibrosis and contributes to electrophysiological changes (2 main factors that can be attenuated by ARB therapy early during the course of the arrhythmia), ARB therapy appears to be a reasonable and safe additive antiarrhythmic intervention. Furthermore, recent systematic meta-analyses\textsuperscript{5,10} suggested that ARB or angiotensin-converting enzyme (ACE) inhibitor therapy may have direct antiarrhythmic effects. In contrast to antiarrhythmic drug trials, in which time to first AF recurrence has been an accepted primary study end point, ARB therapy may take several weeks and months to influence the arrhythmogenic atrial substrate. Therefore, the beneficial effects of ARB therapy may become apparent after long-term therapy only. However, the therapeutic benefit of ARB inhibition has not yet been prospectively investigated in patients with paroxysmal AF in the absence of concomitant ACE-inhibitor and antiarrhythmic therapy. The AFNET (German Network of Competence in Atrial Fibrillation), therefore, conducted the investigator-initiated Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial, a prospective, randomized, placebo-controlled trial analyzing the burden of AF over a 12-month period as the primary study end point in the absence of concomitant ACE inhibitor therapy and systematic use of class I and III antiarrhythmic drugs.

**Methods**

The ANTIPAF trial examined the hypothesis that blocking the angiotensin II type 1 receptor with olmesartan medoxomil (olmesartan) reduces the incidence of episodes of AF in patients with paroxysmal AF during 12 months by >25% compared with standard medication without ARB therapy in a prospective, randomized, placebo-controlled, double-blind trial. The sponsor of the ANTIPAF trial is AFNET, which is funded by the German Ministry of Research and Education. Daiichi Sankyo Deutschland GmbH (Munich, Germany) was the responsible contract research organization for project and data management and was the central core laboratory for the management of all transtelephonic ECG (tele-ECG) devices and the standardized analysis of all transmitted tele-ECGs.

A total of 430 patients were included in the study by 43 centers and were randomized to olmesartan (n=215) or placebo (n=215) and received the study medication (safety population). Of these, 425 (placebo group, n=211; olmesartan group, n=214) had at least 1 readable ECG recording of at least 1 ECG recorded during the 6 months before randomization, age ≥18 years, and written informed consent. Patients were randomized to placebo or 40 mg olmesartan per day. No adjustment of study medication was permitted. Patients with documented paroxysmal AF were stratified by β-blocker use (Figure 1). In case of suspected intolerance of the study medication, study medication was terminated. Study medication was provided by Daiichi Sankyo Deutschland GmbH. Patients were excluded if they had an indication for intervention with an ARB or ACE inhibitor, were on such therapy early during the course of the arrhythmia, ARB therapy appears to be a reasonable and safe additive antiarrhythmic intervention. Furthermore, recent systematic meta-analyses\textsuperscript{5,10} suggested that ARB or angiotensin-converting enzyme (ACE) inhibitor therapy may have direct antiarrhythmic effects. In contrast to antiarrhythmic drug trials, in which time to first AF recurrence has been an accepted primary study end point, ARB therapy may take several weeks and months to influence the arrhythmogenic atrial substrate. Therefore, the beneficial effects of ARB therapy may become apparent after long-term therapy only. However, the therapeutic benefit of ARB inhibition has not yet been prospectively investigated in patients with paroxysmal AF in the absence of concomitant ACE-inhibitor and antiarrhythmic therapy. The AFNET (German Network of Competence in Atrial Fibrillation), therefore, conducted the investigator-initiated Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) trial, a prospective, randomized, placebo-controlled trial analyzing the burden of AF over a 12-month period as the primary study end point in the absence of concomitant ACE inhibitor therapy and systematic use of class I and III antiarrhythmic drugs.

**Study Design**

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A total of 430 patients were included in the study by 43 centers and were randomized to olmesartan (n=215) or placebo (n=215) and received the study medication (safety population). Of these, 425 (placebo group, n=211; olmesartan group, n=214) had at least 1 readable tele-ECG, thus allowing the calculation of the primary end point. By definition, these 425 patients comprised the intention-to-treat population presented in this analysis (Figure 1).

The following terms were used in the study to define outcome parameters. *Day with documented paroxysmal AF*: the calendar day with at least 1 readable ECG recording of ≥30 s duration showing AF. *Documented AF*: an episode of AF in any ECG recording lasting ≥30 s. *Paroxysmal AF*: ECG recordings within 7 consecutive days after initial detection of AF showing both documented AF and sinus rhythm. *Suspected persistent AF*: all ECG recordings within 7 consecutive days after initial detection of AF showing documented AF and initiating an extraordinary visit to perform a Holter monitor recording. *Persistent AF*: a continuous AF in a Holter monitor recording with a minimum of 18 hours readable after suspected persistent AF had been identified.

**Primary End Point**

The primary end point of the study was the percentage of days with documented episodes of paroxysmal or with suspected persistent or
permanent AF. The AF burden was calculated by the number of days with paroxysmal AF or with preceding documentation of suspected persistent AF (up to a maximum of 365 days) divided by the number of measurement days, that is, days in follow-up with at least 1 readable tele-ECG recording (up to a maximum 365 days).

**Secondary Outcome Parameters**

Secondary end points of the study were as follows: (1) time to first occurrence of a documented relapse of AF, (2) quality of life, (3) time to persistent AF, (4) time to prescription of the recovery medication, (5) percentage of days with documented episodes of paroxysmal or with suspected persistent or permanent AF after 90 days of therapy (number of days with paroxysmal AF or with preceding documentation of suspected persistent or permanent AF during follow-up beginning after a treatment wash-in phase of 90 days), (6) number of hospitalizations for cardiovascular reasons according to end point review, (7) number of intermediate medical visits without hospitalization for cardiovascular reasons according to end point review, (8) number of cerebrovascular events, and (9) time to first occurrence of a symptomatic documented episode of AF.

**Permitted Concomitant Medication**

Antihypertensive therapy included diuretics, calcium channel blocking agents, and antiadrenergic substances. The target arterial blood pressure was <140/90 mm Hg for both treatment groups. Oral anticoagulation followed clinical necessity according to present recommendations. A temporary change to intravenous or subcutaneous anticoagulation was permitted. β-blockers were used if therapy was started before study inclusion. The protocol defined amiodarone as recovery medication in case of severe symptoms or heart failure despite sufficient rate control with verapamil or digitals. Furthermore, in the case of persistent rapid AV conduction despite the use of high doses of AV nodal blocking drugs, amiodarone also could be used. Other antiarrhythmic drugs (ion channel blocking drugs) were not permitted.

**Follow-Up**

Patients were asked to record and transmit via telephone at least 1 1-minute ECG per day independent of symptoms. Each patient received his or her personal tele-ECG device for the entire follow-up period. A central core laboratory was used for management of all tele-ECG devices and for the standardized analysis of all transmitted tele-ECGs. Further parameters during follow-up were from a questionnaire of subjective conditions; a quality-of-life questionnaire (SF-12 [Medical Outcomes Study Short Form-12]); serious adverse events; physical examination; noninvasive systemic arterial blood pressure as the mean of 2 measurements; 12-lead ECG at rest; laboratory measurements of sodium, potassium, creatinine, creatine kinase, transaminase, serum urea nitrogen, thyroid stimulating hormone, and international normalized ratio; 24-hour ECG: mean heart rate and rhythm; transthoracic echocardiography; actual medication; and treatment allocation. Questionnaires and follow-up visits were scheduled after 3, 6, 9, and 12 months.

**Sample Size**

The preliminary sample size determination was proposed based on limited knowledge about the distribution of the primary outcome measure. The distribution was expected to be skewed or even J shaped. Therefore, a nonparametric comparison of the primary outcome variable was chosen for the analysis, using a 10% increase compared with the sample size derived from the 2-sided t-test. The results from the SOPAT (Suppression of Atrial Tachyarrhythmias) trial suggested that there is an effect size of one third; that is, the mean difference between the treatments was one third of the SD. A temporary change to intravenous or subcutaneous anticoagulation was permitted. β-blockers were used if therapy was started before study inclusion. The protocol defined amiodarone as recovery medication in case of severe symptoms or heart failure despite sufficient rate control with verapamil or digitals. Furthermore, in the case of persistent rapid AV conduction despite the use of high doses of AV nodal blocking drugs, amiodarone also could be used. Other antiarrhythmic drugs (ion channel blocking drugs) were not permitted.

**Statistical Analysis**

Basic descriptive statistics are presented for the intention-to-treat population and according to treatment assignment. Nominal variables are given as frequencies and percentages. Continuous variables are given as an arithmetic mean and SD. Continuous variables were compared using Student t tests, and categorical variables were compared using χ² tests. Analysis of the primary end point variable was performed by the 2-sided Wilcoxon test, where patients were stratified according to β-blocker treatment (identical to the van Elteren test). For visualization of the distributions of the primary outcome in the 2 groups, a mirror histogram was constructed (Figure 2). Because these distributions turned out to be bimodal, we performed as sensitivity analysis an alternative test approach that goes without any distributional assumptions, a permutation test of the means with 10 000 randomly selected stratwise permutations, and 95% bootstrap CIs based on 10 000 repetitions. For time-to-event secondary outcome variables (parameters 1, 3, 4, and 9), Kaplan-Meier analyses, including log-rank tests, were performed, stratified by β-blocker treatment. Additionally, stratified Cox proportional hazard models were fitted to the data to calculate hazard ratios and cumulative event rates for quantification and visualization of treatment effects. For the other secondary outcome variables (parameters 5, 6, 7, and 8), 2-sided Wilcoxon tests were performed, where patients were stratified according to β-blocker treatment analog to the prespecified analysis of the primary outcome. Quality-of-life data (SF-12 questionnaire, parameter 2) were analyzed using ANCOVA with baseline adjustment. The probability of type I error was fixed to 5% 2 sided and not adjusted for multiplicity of secondary end points. Instead, the secondary end points were hierarchically ordered as previously given to allow for an extension of a claim beyond the primary hypothesis (closed testing procedure).

Three post hoc analyses were performed for further exploration of treatment effects. First, it was systematically tested whether there were differential treatment effects between the β-blocker strata. Second, for time-to-event end points, we checked the proportional hazards assumption by introducing a treatment×log(time) interaction as a time-dependent covariate to the Cox models and tested by likelihood ratio tests whether the models were significantly improved by assuming different time trends for the treatments. Third, because the use of recovery medication may have diluted other treatment effects, a subanalysis of the primary end point only considering patients without recovery medication was performed. Stata version 11.0, SAS for Windows version 9.2, and R version 2.8 software were used for the statistical analyses.

**Results**

Baseline characteristics of the intention-to-treat population are given in Table 1. At the end of follow-up, systolic blood pressures (placebo, 131.3 ± 16.3 mm Hg; olmesartan,
131.4±19.1 mm Hg; \( P=0.863 \)) and diastolic blood pressures (placebo, 80.4±8.9 mm Hg; olmesartan, 78.5±10.2 mm Hg; \( P=0.096 \) adjusted for baseline values) remained comparable in the 2 groups. Medical therapy was balanced and did not change significantly in either group up to the end of follow-up.


### Tele-ECG Recordings

A total of 97 159 tele-ECGs were recorded in the 425 patients during follow-up. A total of 87 818 tele-ECGs (placebo group, \( n=44,888 \); olmesartan group, \( n=42,930 \)) could be used for analyses. The number of tele-ECGs not fulfilling quality criteria in the blinded analysis was 9,341 (9.6%) and could not be used for further analyses. Thus, a mean of 207 tele-ECGs were recorded per patient, with an average of 1.12 tele-ECGs per patient and measurement day.


### Primary End Point

Figure 2 shows the distributions of the primary end point of AF burden by treatment. Both distributions are very similar and reveal an essential bimodality with a marked mode at small AF

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (( n=211 ))</th>
<th>Olmesartan (( n=214 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.9±10.2</td>
<td>61.1±11.2</td>
<td>0.470</td>
</tr>
<tr>
<td>Women</td>
<td>95 (45.0)</td>
<td>81 (37.9)</td>
<td>0.133</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>103 (48.8)</td>
<td>106 (49.5)</td>
<td>0.882</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18 (8.5)</td>
<td>17 (7.9)</td>
<td>0.826</td>
</tr>
<tr>
<td>History of smoking</td>
<td>91 (43.1)</td>
<td>91 (42.5)</td>
<td>0.900</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>17/201 (8.5)</td>
<td>11/205 (5.4)</td>
<td>0.218</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>0.596</td>
</tr>
<tr>
<td>0</td>
<td>196/211 (92.9)</td>
<td>197/212 (92.9)</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>8/211 (3.8)</td>
<td>6/212 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>6/211 (2.8)</td>
<td>9/212 (4.2)</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>1/211 (0.5)</td>
<td>0/212 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>0/211 (0.0)</td>
<td>0/212 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>63.3±7.7</td>
<td>63.2±7.8</td>
<td>0.866</td>
</tr>
<tr>
<td>Left atrial diameter &gt;40 mm</td>
<td>68/196 (34.7)</td>
<td>75/205 (36.6)</td>
<td>0.693</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.88±0.21</td>
<td>0.92±0.20</td>
<td>0.049</td>
</tr>
<tr>
<td>Serum urea nitrogen, mg/dL</td>
<td>31.0±17.4</td>
<td>32.8±16.0</td>
<td>0.259</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta )-blocker (stratum)</td>
<td>149/211 (70.6)</td>
<td>152/214 (71.0)</td>
<td>0.926</td>
</tr>
<tr>
<td>Dihydropyridines</td>
<td>23/162 (14.2)</td>
<td>23/170 (13.5)</td>
<td>0.860</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>1/162 (0.6)</td>
<td>1/170 (0.6)</td>
<td>0.973</td>
</tr>
<tr>
<td>Class IV antiarrhythmic agent</td>
<td>6/162 (3.7)</td>
<td>8/170 (4.7)</td>
<td>0.649</td>
</tr>
<tr>
<td>Verapamil</td>
<td>5/162 (3.1)</td>
<td>7/170 (4.1)</td>
<td>0.614</td>
</tr>
<tr>
<td>Ca antagonist</td>
<td>29/162 (17.9)</td>
<td>30/170 (17.7)</td>
<td>0.952</td>
</tr>
<tr>
<td>Diuretics</td>
<td>24/162 (14.8)</td>
<td>22/170 (12.9)</td>
<td>0.621</td>
</tr>
<tr>
<td>Nitrates</td>
<td>3/162 (1.9)</td>
<td>2/170 (1.2)</td>
<td>0.613</td>
</tr>
<tr>
<td>Statins</td>
<td>25/162 (15.4)</td>
<td>16/170 (9.4)</td>
<td>0.095</td>
</tr>
<tr>
<td>ASS</td>
<td>48/162 (29.6)</td>
<td>53/170 (30.6)</td>
<td>0.849</td>
</tr>
<tr>
<td>OAC</td>
<td>46/162 (28.4)</td>
<td>36/170 (20.6)</td>
<td>0.127</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>64.3±11.8</td>
<td>64.0±12.6</td>
<td>0.749</td>
</tr>
<tr>
<td>Systolic RR, mm Hg</td>
<td>132.5±18.7</td>
<td>130.0±18.3</td>
<td>0.210</td>
</tr>
<tr>
<td>Diastolic RR, mm Hg</td>
<td>79.9±10.2</td>
<td>78.2±8.6</td>
<td>0.098</td>
</tr>
<tr>
<td>CHADS(_2) score*</td>
<td>0.5 (0–4)</td>
<td>0 (0–4)</td>
<td>0.7±0.9</td>
</tr>
<tr>
<td>CHA(_2)DS(_2)-VASc score*</td>
<td>1 (0–7); 1.6±1.4</td>
<td>1 (0–6); 1.5±1.3</td>
<td>0.5605</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or n (%) [or n/total no. (%)], unless otherwise indicated. The \( t \) test was used for continuous variables, and Pearson \( \chi^2 \) test with continuity correction was used for categorical variables.

NYHA indicates New York Heart Association; ASS, aspirin; OAC, oral anticoagulants; CHADS\(_2\), congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack; CHA\(_2\)DS\(_2\)-VASc, congestive heart failure or left ventricular systolic dysfunction), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74 years, sex category; systolic RR, systolic blood pressure; diastolic RR, diastolic blood pressure.

*For CHADS\(_2\) and CHA\(_2\)DS\(_2\)-VASc scores, median (range) and mean±SD are given. Groups were compared using Wilcoxon-Mann-Whitney test.
burdens up to 10%, but >0, and a smaller mode at AF burdens >90%, resulting in an unexpectedly high SD (pooled SD, 0.262). The means were 14.7% in the placebo group and 15.1% in the olmesartan group and were not significantly different in the prespecified analysis (P=0.77) or in the sensitivity analysis (P=0.865) (Table 2). Because of the bimodality of distributions, bootstrap confidence limits may be more reliable than t-test-based confidence limits. The 95% CIs of the difference between olmesartan and placebo based on bootstrapping were large, allowing for absolute differences of −4.5% and +5.4% or, with respect to a mean AF burden of 14.9%, for relative differences of −31% or 37%.

Secondary Outcome Parameters

The secondary outcome parameters are listed in Table 2. With one exception, secondary outcomes did not differ between treatment groups. Time to prescription of recovery medication (amiodarone) tended to be shorter in the placebo group (P=0.26). Recovery medication was initiated in 9 (4.2%) patients in the olmesartan group and 20 (9.5%) patients in the placebo group. In any case, because the primary end point was not significant, no claim for an advantage of olmesartan in secondary outcomes can be derived from the data because of the prespecified hierarchical order of hypotheses.

Post Hoc Analyses

In the first post hoc analysis, only the time to prescription of recovery medication revealed significant differences in treatment effects between β-blocker strata. The tendency to fewer prescriptions of amiodarone was only present if patients were on β-blocker therapy (no β-blocker hazard ratio, 1.09 [95% CI, 0.15–7.73]; β-blocker hazard ratio, 0.34 [95% CI, 0.14–0.83]; P=0.041). In the second post hoc analysis, treatment×log(time) interactions were found for time to first occurrence of a documented relapse of AF (P=0.004) (Figure 3), time to prescription of the recovery medication (P=0.00), and time to first occurrence of a symptomatic documented episode of AF (P=0.004). In each of these end points, survival curves were crossing, with a significant trend toward better values at the end of the observation interval in the olmesartan group (Figure 3).

It could be argued that the difference in recovery medication favored the placebo group in the primary analysis of AF burden. Thus, we performed a third post hoc sensitivity analysis, exclud-

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**Table 2. Primary End Point and Secondary Outcome Parameters**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Description</th>
<th>Placebo [Mean (95% CI)]</th>
<th>Olmesartan [Mean (95% CI)]</th>
<th>Olmesartan vs Placebo Difference, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td>Percentage of days of AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prespecified analysis*</td>
<td>14.7 (10.9 to 18.4)</td>
<td>15.1 (11.4 to 18.8)</td>
<td>0.4 (−4.6 to 5.5)</td>
<td>0.770†</td>
<td></td>
</tr>
<tr>
<td>Sensitivity analysis*</td>
<td>14.7 (11.0 to 18.3)‡</td>
<td>15.1 (11.7 to 18.5)‡</td>
<td>0.4 (−4.5 to 5.4)‡</td>
<td>0.865§</td>
<td></td>
</tr>
<tr>
<td>Secondary end points</td>
<td>Percentage of days of AF after a treatment wash-in phase of 90 d*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11.3 (8.0 to 14.5)</td>
<td>12.0 (8.6 to 15.4)</td>
<td>0.7 (−3.8 to 5.2)</td>
<td>0.563†</td>
<td></td>
</tr>
<tr>
<td>No. hospitalizations for cardiovascular reasons according to end point review†</td>
<td>0.17 (0.06 to 0.28)</td>
<td>0.19 (0.09 to 0.30)</td>
<td>0.02 (−0.12 to 0.17)</td>
<td>0.958†</td>
<td></td>
</tr>
<tr>
<td>No. intermediate medical visits without hospitalization for cardiovascular reasons according to end point review*</td>
<td>1.87 (1.31 to 2.43)</td>
<td>1.84 (1.28 to 2.40)</td>
<td>−0.03 (−0.79 to 0.73)</td>
<td>0.127†</td>
<td></td>
</tr>
<tr>
<td>No. cerebrovascular events*</td>
<td>0.007 (−0.004 to 0.019)</td>
<td>0.003 (−0.009 to 0.014)</td>
<td>−0.005 (−0.021 to 0.011)</td>
<td>0.265†</td>
<td></td>
</tr>
<tr>
<td>Quality of life: SF-12 physical sum scores*</td>
<td>45.6 (44.0 to 47.1)</td>
<td>45.1 (43.6 to 46.7)</td>
<td>−0.5 (−2.6 to 1.7)</td>
<td>0.678</td>
<td></td>
</tr>
<tr>
<td>Quality of life: SF-12 mental sum scores*</td>
<td>50.8 (49.1 to 52.6)</td>
<td>52.5 (50.7 to 54.2)</td>
<td>1.6 (−0.7 to 4.0)</td>
<td>0.173</td>
<td></td>
</tr>
<tr>
<td>Cumulative Event Rate at 12-mo Placebo, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to first occurrence of a documented relapse of AF¶</td>
<td>78.5</td>
<td>76.8</td>
<td>1.031 (0.828 to 1.283)</td>
<td>0.786¶</td>
<td></td>
</tr>
<tr>
<td>Time to persistent AF¶</td>
<td>9.0</td>
<td>9.2</td>
<td>1.080 (0.571 to 2.042)</td>
<td>0.812¶</td>
<td></td>
</tr>
<tr>
<td>Time to prescription of the recovery medication</td>
<td>8.8</td>
<td>3.4</td>
<td>0.410 (0.186 to 0.904)</td>
<td>0.022¶</td>
<td></td>
</tr>
<tr>
<td>Time to first occurrence of a symptomatic documented episode of AF¶</td>
<td>70.9</td>
<td>63.9</td>
<td>0.868 (0.685 to 1.100)</td>
<td>0.240¶</td>
<td></td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; SF-12, Medical Outcomes Study Short Form-12.
*Strata adjusted mean values are shown. †Van Elteren test. ‡Calculations were performed per bootstrapping, 10 000 repetitions. §Permutation test with 10 000 realizations. ¶Adjusted estimates from stratified Cox model. †Stratified log-rank test.
cardiac infarction. Other serious adverse events in the olmesartan group were 1 acute myocardial infarction in the course of heavy physical exercise after he had experienced significant dyspnea and fatigue for some days; his left ventricular ejection fraction at baseline was 56% without history of coronary artery disease. Other serious adverse events in the placebo group were 1 episode of a nonsustained wide-QRS complex tachycardia (12 beats), 1 supraventricular tachycardia, 1 septic shock with acute respiratory distress syndrome, and 1 carcinoma of the pancreas. In all adverse events adjudicated as serious, the committee saw no relationship to the study medication. In summary, the safety profile of the olmesartan group showed no difference compared with the placebo group.

### Serious Adverse Events

Sixty-five serious adverse events were reported by investigators and assessed by the blinded critical event committee. Forty-one of the events were classified as nonserious, whereas 24, which occurred in 21 patients, were classified as serious adverse events according to ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) good clinical practice guidelines (Table 3). No significant differences were found between groups. There were 3 deaths in the trial. One 62-year-old patient in the placebo group died of carcinoma of the pancreas. Two deaths occurred in the olmesartan group. One 69-year-old patient died of an assumed acute myocardial infarction in the course of heavy physical exercise after he had experienced significant dyspnea and fatigue for some days; his left ventricular ejection fraction at baseline was 56% without history of coronary artery disease. The other patient was a 74-year-old woman who died suddenly without preceding clinical symptoms. She had diabetes mellitus type II and a moderately reduced left ventricular ejection fraction at baseline without a history of coronary artery disease. Other serious adverse events in the placebo group were 1 acute pancreatitis, 2 supraventricular tachycardias, and 1 acute myocardial infarction. Other serious adverse events in the olmesartan group were 1 episode of a nonsustained wide-QRS complex tachycardia (12 beats), 1 supraventricular tachycardia, 1 septic shock with acute respiratory distress syndrome, and 1 carcinoma of the pancreas. In all adverse events adjudicated as serious, the committee saw no relationship to the study medication. In summary, the safety profile of the olmesartan group showed no difference compared with the placebo group.

### Discussion

The ANTIPAF trial showed that the use of 40 mg olmesartan in patients with paroxysmal AF is safe but does not reduce the AF burden compared with placebo during 1-year follow-up. Furthermore, 8 of 9 defined secondary outcome parameters, such as quality of life, time to first symptomatic and asymptomatic recurrence of AF, time to persistent AF, and number of hospitalizations for cardiovascular reasons, were not different between groups. Although in the presence of β-blocker prescriptions, time to prescription of the recovery medication (amiodarone) tended to be shorter in the placebo group, the primary end point (AF burden) was still comparable in a subanalysis restricted to patients not receiving the recovery medication. In any case, because the primary end point was not significant, no claim for an advantage of olmesartan in secondary outcomes can be derived from the data due to the prespecified hierarchal order of hypotheses.

Most patients with AF have concomitant cardiovascular diseases like hypertension, heart failure, or valvular heart disease. Such diseases usually generate a clear indication for ACE inhibitor or ARB therapy, which have been shown to be effective and safe. In addition to ventricular changes, these cardiovascular diseases have been found to affect substantially the structure of atrial tissue and, thereby, the occurrence of AF. At the molecular level, angiotensin II, oxidative stress, and proinflammatory mediators are of particular importance to induce proarrhythmic structural remodeling and atrial ectopy in the area of the pulmonary veins. Therefore, the use of ACE inhibitors or ARBs appears as an attractive approach to treat patients with AF. Experimental data and several clinical trials support this concept; however, previous studies suggest that the concept to prevent structural atrial remodeling is more efficient for primary prevention of
AF, especially in patients with concomitant cardiovascular diseases.\(^5\),\(^10\),\(^17\)–\(^20\)

For secondary prevention, the results are conflicting.\(^5\),\(^10\),\(^21\)–\(^26\)

First, prospective studies examined the effect of ARBs and ACE inhibitors in association with amiodarone to prevent AF.\(^5\),\(^21\),\(^22\),\(^26\)

Of note, Madrid et al\(^27\) found a dose-dependent effect of irbesartan on AF recurrence in 120 patients after cardioversion. However, these trials were relatively small, and systematic ECG monitoring to detect silent AF was not used.\(^21\)–\(^23\) In contrast, the GISSI-AF [Giuppo Italiano per Lo Studio della Sopravvenza nell’Infarto Mioccondiso-Atrial Fibrillation] trial showed no effect of ARB therapy on the recurrence of AF in >1400 patients with underlying cardiovascular diseases, diabetes mellitus, or left atrial enlargement. However, the study did not exclude patients on ACE inhibitor therapy.\(^24\) Approximately 60% of all patients received concomitant ACE inhibitor therapy. Negative results were also found in a recent retrospective subanalysis of ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which examined baseline prevalence and in-trial incidence of new-onset AF or atrial flutter and their influence on clinical outcomes in 42 418 men and women with hypertension aged >55 years with at least 1 additional cardiovascular risk factor. AF/atrial flutter occurred in 641 (2.0%) participants and, excluding doxazosin, did not differ by antihypertensive treatment group (lisinopril, amloidpine, and thiazide-like diuretics).\(^28\) Of note, in the high-risk hypertensive population, preexisting and new-onset AF/atrial flutter were associated with increased mortality. Similar to the ANTIPAF results, ALLHAT raised substantial questions about whether previous studies suggesting lower new-onset AF/atrial flutter rates with ACE inhibitors or ARBs are generalizable. In accordance, the ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) program and ONTARGET (ONGoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) also could not show positive effects of ARBs on the occurrence of AF in patients with cardiovascular risk factors.\(^25\),\(^29\)

Nevertheless, meta-analyses still favor the use of ACE inhibitors and ARBs to reduce the occurrence of AF.\(^5\),\(^10\) A recent meta-analysis included 23 randomized controlled trials of 87 048 patients.\(^15\) In primary prevention, 6 trials in hypertension, 2 trials in myocardial infarction, and 3 trials in heart failure were included (some being post hoc analyses of randomized controlled trials). In secondary prevention, 8 trials after cardioversion and 4 trials assessing the medical prevention of recurrence were included. Overall, renin-angiotensin system inhibition reduced the odds ratio for AF by 33%, but there was substantial heterogeneity among trials. In primary prevention, renin-angiotensin system inhibition was effective in patients with heart failure and in those with hypertension and left ventricular hypertrophy but not in patients postmyocardial infarction overall. In secondary prevention, renin-angiotensin system inhibition often was administered in addition to antiarrhythmic drugs, including amiodarone, further reducing the odds for AF recurrence after cardioversion by 45% and in patients on medical therapy by 63%. Thus, it appears that ARBs or ACE inhibitors may be effective in the setting of structural heart disease through their inherent action on the renin-angiotensin system and, in particular, if combined with amiodarone.

On the basis of existing data, it remained to be determined whether ARBs or ACE inhibitors per se have an antiarrhythmic effect, which should be tested in patients with AF in the absence of structural heart disease, where AF often may depend on ectopic activity mostly originating from the pulmonary veins. To our knowledge, the ANTIPAF trial, is the first study to evaluate the role of ARBs for secondary prevention in patients with paroxysmal AF without significant cardiovascular diseases in the absence of ACE inhibitors and ion channel blocking antiarrhythmic drug therapy. A major effort was undertaken to document AF recurrences during the follow-up period by daily tele-ECG monitoring. Because it was assumed that it may take several weeks to months for ARBs to modulate atrial structure and electrophysiology, the primary outcome parameter was not the first recurrence of AF but of AF burden, which is clinically more important for the patient. Thus, the duration of follow-up was extended far beyond the first recurrence of AF. In addition, not only the occurrence of symptomatic AF was identified (secondary outcome parameter), but also any type of recurrence independent of symptoms was counted in the primary end point. During 1-year follow-up, the ANTIPAF trial failed to show an antiarrhythmic effect of olmesartan. Even after exclusion of the first 90 days of therapy, which appears as a sufficient time period for ARBs to affect proarrhythmic structural and molecular atrial changes, ARB therapy had no influence on the recurrence of AF. In addition, the time to persistent AF was not altered. So far, it was concluded from many studies that ARBs might reduce or abolish atrial remodeling processes and, thereby, attenuate the progression from paroxysmal to persistent AF. However, and in clear contrast to experimental and first clinical findings, the present study showed that the progression of AF from paroxysmal to persistent AF was not altered by ARB therapy. This cannot be explained by an inadequate dosage of olmesartan because the ANTIPAF trial used the highest permitted dose of the drug. Thus, it appears highly unlikely that the overall results of the trial are caused by insufficient drug effects or by differences of concomitant factors like systemic blood pressure. Of note, the present data set (including >80 000 tele-ECGs) shows very high variability of AF recurrences in patients with paroxysmal AF. Thus, it appears very unlikely that nonsystematic and intermittent ECGs or Holter monitor recordings can assess the true burden of AF. This finding should be considered in future attempts to assess the efficacy of pharmacological and nonpharmacological antiarrhythmic approaches. The only parameter that was found to be different in the 2 study groups was the time to prescription of the recovery medication (amiodarone), which was given earlier and more frequently in the placebo group, and is consistent with the observation that patients with recovery medication, on average, had more AF burden. However, AF burden in the 2 treatment groups was still comparable when the 29 patients who received recovery medication were excluded from analysis. The recovery medication was allowed in the present study because it was believed to be unethical to compare ARB therapy with placebo in patients with symptomatic AF over an extended period without a possibility for an accepted and effective antiarrhythmic therapy. Therefore, the recovery medication (amiodarone) was included in the
protocol. The initiation of amiodarone therapy was prespecified as a secondary outcome parameter in the trial. As assumed, patients with recovery medication had more AF episodes compared with others. Nevertheless, the absolute number of patients receiving the recovery medication was low, and the primary outcome was unchanged.

In summary, results of recent clinical trials do not support the use of ARBs or ACE inhibitors in patients with AF without concomitant structural heart disease. These findings have influenced the 2010 European Society of Cardiology AF guidelines,\(^{30}\) which do not recommend upstream therapy with ACE inhibitors and ARBs for prevention of AF in patients without cardiovascular disease. Thus, the present results of the ANTIPAF trial clearly support this recommendation.

Limitations
A limitation of the study is that there was an essential bimodality in both groups: AF burden was rather low in most study patients and very high in a small subgroup (Figure 2). Thus, the power of the study was smaller than anticipated, and true improvements and deteriorations of the average AF burden of up to 30% cannot be excluded. Nevertheless, the study shows that the recurrence of AF is highly variable, and therefore, the true burden of AF is difficult to predict. Continuous monitoring for extended periods (>1 year) with implanted devices and analyses of very large patient populations might be the only way to determine mild or modest differences among patients with paroxysmal AF. Nevertheless, the use of daily tele-ECGs is in accordance with a recommended monitoring strategy in AF trials.\(^ {31} \) It is conceivable, however, that long-term therapy with ARBs over several years may produce a long-term antiarrhythmic effect in patients with AF without structural heart disease. The survival curves reveal trends that suggest possible differences beyond the time interval studied (Figure 3).

Conclusions
ARB therapy per se does not reduce the number of AF episodes in patients with documented paroxysmal AF without structural heart disease during 1-year follow-up. Therefore, ARBs may not be recommended as first-line treatment in this clinical setting if not indicated for other reasons.

Acknowledgments
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Disclosures
Dr Goette has received speaker fees from Daiichi Sankyo Deutschland GmbH.

References
CLINICAL PERSPECTIVE

Several post hoc analyses from clinical trials suggest that upstream therapy with angiotensin II receptor blockade (ARB) is beneficial in patients with atrial fibrillation (AF). So far to our knowledge, a proof-of-principle study showing that ARBs have true antiarrhythmic potential has not been published. The ANTIPAF (Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation) trial is the first prospective, randomized, placebo-controlled, multicenter trial analyzing the AF burden (percentage of days with documented episodes of paroxysmal AF) during a 12-month follow-up as the primary study end point. Four hundred twenty-five patients were followed using daily transtelephonic ECG recordings independent of symptoms. The extensive number of 87,818 transtelephonic ECGs were analyzed during follow-up. The primary end point (AF burden) as well as secondary end points were not different in the 2 treatment groups. Thus, 1 year of ARB therapy per se did not reduce the number of AF episodes in patients with documented paroxysmal AF without structural heart disease. In contrast to GISSI-AF and the ACTIVE (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) program, no concomitant use of angiotensin-converting enzyme inhibitors and antiarrhythmic drugs was allowed in ANTIPAF. Therefore, the ANTIPAF study proves that upstream therapy with ARB per se does not reduce the recurrence rate of AF. In the clinical setting, ARB should only be used in patients with AF if these substances are indicated for therapy of concomitant diseases like hypertension and heart failure.
Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF) Trial
Andreas Goette, Norbert Schön, Paulus Kirchhof, Günter Breithardt, Thomas Fetsch, Karl Georg Häusler, Helmut U. Klein, Gerhard Steinbeck, Karl Wegscheider and Thomas Meinertz

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A. Goette and T. Meinertz (PI), G. Breithardt, T. Fetsch, H.U. Klein, G. Steinbeck

Data and Safety Monitoring Committee:
L. Seipel, Tübingen (Chairman); D. Andresen, Berlin; M. Gottwik, Nürnberg

Biometrical advisor: K. Wegscheider

Critical Event Committee (CEC):
M. Oeff, U. Tebbe, G. Einhäuserl, K.G. Häusler

Participating and recruiting centres (number of included patients)
Praxis Dr. Schön, Mühldorf (95) N Schön; Universitätsklinikum Magdeburg, Magdeburg (74)
A Goette, A D’Allessandro, M Hammwöhner; Universitätsklinikum Münster, Münster (33) G Breithardt, P Kirchhof, S Müller, S Orwat, A Samol; Euregio Klinik Nordhorn, Nordhorn (26) M-L Leutermann-Oeinck; Uniklinik Bonn, Bonn (18) T Lewalter, S Remerie; Praxis Dr. Boscher, Biberach an der Riß (18) D Boscher; Praxis Dr. Sarnighausen, Lüneburg (12) H-E Sarnighausen; Praxis Dr. Taggeselle, Markkleeberg (11) J Taggeselle; Universitätsklinikum Hamburg-Eppendorf, Hamburg (10) T Meinertz, I Drewitz; Praxis Dr. AL-Zoebi, Wermsdorf (10) A Al-Zoebi; Uniklinik Mannheim, Mannheim (9) C Echtert, M Werle; Klinik Bassum, Bassum (9) B Hayen; Klinik Urban Berlin, Berlin (8) A Mielke; Uniklinik Aachen, Aachen (7) T Schimpf, E Saygili; Reha Zentrum Spreewald, Burg (7) W Kamke; Praxis Dr. Jahnke, Ulm (7) N Jahnke; Praxis Dr. Haßler, Plauen (7) N Haßler; Praxis Dr. Gabelmann, Kirchzarten (7) M Gabelmann; Klinikum Kassel, Kassel (6) J Neuzner; Städt. Klinik Brandenburg, Brandenburg (5) C Sprenger; Uniklinik Tübingen, Tübingen (5) N Rüb, A Henning; Robert Bosch Krankenhaus, Stuttgart (5) U Parade, C Holzer; Praxis Dr. Klingenhoeber, Bonn (4) T Klingenhoeber; Praxis Dr. Weimer, Reinfeld (3) J Weimer; Praxis Dr. Jeserich, Nürnberg (3) M Jeserich; Praxis Dr. Berg, Ühlingen (3) R Berg; Krankenhaus Hagenow, Hagenow (3) D Buchholz; Ahrtalklinik Bad Bodendorf, Bad Bodendorf (3) G Giesen; Herzzentrum Leipzig, Leipzig (2) G Hindricks; Praxis Dr. Schumacher, Wolmirstedt (2) M Schumacher; Praxis Dres. Kruck/ Bosch, Ludwigsburg (2) R Bosch; Praxis Dr. Killat, Haßloch (2) H Killat; Krankenhaus Wriezen, Wriezen (2) L Gruev; Katharinen Hospital Unna, Unna (2) S Atri; Klinik Pirna, Pirna (1) B Axthelm; Klinik Garmisch-Partenkirchen, Garmisch-Partenkirchen (1) M Adelt; Evangelisches Krankenhaus Düsseldorf, Düsseldorf (1) E Vester; Clemenshospital Münster, Münster (1) B Knipper; Herzzentrum Lahr, Lahr (1) E von Hodenberg; Hellmig Krankenhaus Kamen, Kamen (1) HJ Dieckmann; Praxis Dr. Baar, Andernach (1) W Baar; Praxis Dr. Neubert, Rathenow (1) J Neubert; Praxis Dr. Schaefer, Aachen (1) P Schaefer; Praxis Dr. Ulrich, Kamen (1) C Ulrich.