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

Running title: Goette et al.; The ANTIPAF Trial

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Trial results were presented at the HOT Line Session III at the ESC congress 2010 in Stockholm.
Abstract:

**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) has so far only been shown in patients with structural heart disease. Here, we report the primary outcome of the ANTIPAF trial, which investigated the effect of olmesartan medoxomil as compared to 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 endpoint. 430 patients with documented paroxysmal AF without structural heart disease were randomized to placebo or 40mg olmesartan per day. Concomitant therapy with ARBs, ACE inhibitors, and antiarrhythmic drugs was prohibited. Patients were followed using daily trans-telephonic ECG recordings independent of symptoms. The intention-to-treat population of the trial encompassed 425 patients (211 placebo group and 214 olmesartan group). A total of 87,818 tele-ECGs were analysed in these patients during follow-up (44,888 ECGs in the placebo group and 42,930 ECGs in the olmesartan group). Thus, a mean of 207 tele-ECGs were recorded per patient. The primary endpoint (AF burden) was not different in the two groups (p=0.770). Secondary outcome parameters including quality of life were also not different in both groups. In particular, time to first AF recurrence, time to persistent AF, and number of hospitalizations were not different in the two 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 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://clinicaltrials.gov. Unique identifier: NCT 00098137

**Key words:** angiotensin, arrhythmia, atrial fibrillation, remodeling, olmesartan, telemedicine
Introduction

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).

Pharmacological inhibition of the renin-angiotensin system improves survival in patients with structural heart disease and is clearly a safe intervention in most patients with AF (5,6). There is good experimental evidence that ARB therapy can prevent structural remodelling (6-9) and occurrence of AF in patients with structural heart disease (5,10,11). Given the observation that AF induces atrial fibrosis and contributes to electrophysiologic changes, - two main factors that can be attenuated by ARB therapy early during the course of the arrhythmia - ARB therapy appears as a reasonable and safe additive antiarrhythmic intervention. Furthermore, recent systematic meta-analyses (5,10) suggest that ARB or 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 endpoint, 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 suffering from paroxysmal AF in the absence of concomitant ACE-inhibitor and antiarrhythmic therapy.

The German Atrial Fibrillation Competence NETwork (AFNET) therefore conducted the investigator-initiated Angiotensin II-Antagonist in Paroxysmal Atrial Fibrillation (ANTIPAF)-Trial as a prospective, randomized, placebo-controlled trial analyzing the burden of AF over a
12-month period as the primary study endpoint in the absence of concomitant ACE-inhibitor therapy and systematic use of class I and III antiarrhythmic drugs.

Methods

Study design

The ANTIPAF trial was designed to examine 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 more than 25% compared to standard medication without ARB therapy in a prospective, randomized, placebo-controlled, double-blind trial. Sponsor of the ANTIPAF Trial is the German Network of Competence in Atrial Fibrillation, which is funded by the German Ministry of Research and Education (BMBF). Daiichi Sankyo Deutschland GmbH (Munich, Germany) provided an unrestricted grant to support the study. The rationale and trial design has previously been published (12). In brief, patients were eligible to participate in the study if they had documented paroxysmal AF (ECG documentation of AF at least in one ECG recorded during the last 6 months prior to randomization), age ≥ 18 years, and written informed consent. Patients were randomized to placebo or 40mg olmesartan per day. No adjustment of study medication was permitted. Patients with documented paroxysmal AF were stratified by beta-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 therapy with an ARB or ACE inhibitor, were on such therapy within the last month, or had received therapy with antiarrhythmic agents (sodium or potassium channel blockers within four half-lives; amiodarone within the last 3 months). Other exclusion criteria were direct-current cardioversion within the
last 3 months, symptomatic bradycardia, implanted pacemaker or implanted cardioverter/defibrillator with any antitachycardiac algorithm in use, cardiac surgery or cardiac catheter ablation within the last 3 months, typical angina pectoris symptoms at rest or during exercise, known coronary artery disease with indication for intervention, significant valvular disease, left ventricular ejection fraction < 40%, diastolic blood pressure > 110mm Hg at rest, symptomatic arterial hypotension, known renal artery stenosis, serum creatinine > 1.8 mg/dl, relevant hepatic or pulmonary disorders, hyperthyreosis manifested clinically or in laboratory, known drug intolerance for ARB, females who were pregnant or breast feeding, females of childbearing potential who were not using a scientifically accepted method of contraception, participation in a clinical trial within the last 30 days, drug addiction or chronic alcohol abuse, and legal incapacity, or other circumstances which would prevent the patient from understanding the aim, nature or extent of the clinical study. The Institute for Clinical Cardiovascular Research (IKKF), Munich, was the responsible CRO for project and data management. IKKF was additionally the central core lab for management of all Tele-ECG devices and for the standardized analysis of all transmitted telemetric ECGs.

A total of 430 patients were included in the study by 43 centres and were randomized to olmesartan (215) or placebo (215) and received the study medication (safety population). Of these, 425 (211 patients in the placebo group and 214 patients in the olmesartan group) had at least one evaluable tele-ECG and thus allowed the calculation of the primary endpoint. By definition, these 425 patients constitute the intention-to-treat (ITT) population to be presented in this analysis (Figure 1).

The following definitions were used in the study to define outcome parameters. Day with documented paroxysmal atrial fibrillation: Calendar day with at least one readable ECG re-
cording of ≥ 30 seconds duration showing AF. Documented atrial fibrillation: Episode of atrial fibrillation in any ECG recording lasting longer than 30 sec. Paroxysmal atrial fibrillation: ECG recordings within 7 consecutive days after initial detection of atrial fibrillation show both, documented AF and sinus rhythm. Suspected persistent atrial fibrillation: All ECG recordings within 7 consecutive days after initial detection of AF show documented AF, which initiates an extraordinary visit to perform a Holter recording. Persistent atrial fibrillation: Continuous AF in a Holter recording with a minimum of 18 hours readable after suspected persistent AF has been identified.

Primary endpoint

The primary endpoint 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 maximum 365 days) divided by the number of measurement days, i.e. days in follow-up with at least one readable tele-ECG recording (up to maximum 365 days).

Secondary outcome parameters

Secondary endpoints of the study were: 1. Time to first occurrence of a documented relapse of atrial fibrillation. 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 cardiovas-
cular reasons according to endpoint review. 7. Number of intermediate medical visits without hospitalization for cardiovascular reasons according to endpoint review. 8. Number of cerebrovascular events. 9. Time to first occurrence of a symptomatic documented episode of AF.

**Permitted concomitant medication**

Antihypertensive therapy: Diuretics, calcium channel blocking agents, antiadrenergic substances. The target arterial blood pressure was < 140/90mmHg for both treatment groups. Anticoagulation: Oral anticoagulation should follow clinical necessity according to present recommendations (13). A temporary change to i.v. or s.c. anticoagulation was permitted. Beta-blocker, if therapy 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 and/or digitalis. Furthermore, in the case of persistent rapid AV conduction despite the use of high doses of AV nodal blocking drugs, amiodarone could be used as well. Other antiarrhythmics (ion channel blocking drugs) were not permitted.

**Follow-up**

Patients were asked to record and transmit via telephone at least one 1-minute ECG per day independent of symptoms. Each patient received his/her personal tele-ECG device for the entire follow-up period. A central core lab 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 included in a questionnaire of subjective conditions; quality of life questionnaire (SF-12); serious adverse events; physical examination; non-invasive systemic arterial blood pressure, as mean of two measurements; 12-lead ECG at rest; laboratory: sodium, potassium, creatinine, creatine
kinase, transaminases, BUN, TSH, INR; 24-hour ECG: mean heart rate and rhythm; transthoracic echocardiography; actual medication; treatment allocation. Questionnaires and follow-up visits were scheduled after 3, 6, 9, and 12 months.

Sample size
The preliminary sample size determination had been proposed based on rather limited knowledge about the distribution of the primary outcome measure. The distribution had to be expected to be rather skewed or even J-shaped. Therefore, a nonparametric comparison of the primary outcome variable was chosen for the analysis using a 10% increase as compared to the sample size derived from the two-sided t-test. The results from the SOPAT trial suggested that there is an effect size of $1/3$, i.e. the mean difference between the treatments being a third of the standard deviation. A total of 382 patients are required to detect this difference in a two-sided t test with a significance level of $\alpha=0.05$ with a power of 90% (Program N, IDV Gauting, Germany). The 10% increase for the non-parametric approach would then result in a total of 422 evaluable patients (211 per group).

Statistical analysis
Basic descriptive statistics are presented for the ITT population, and according to treatment assignment. Nominal variables are given as frequencies and percentages. Continuous variables are given as arithmetic mean and standard deviation. Continuous variables were compared using Student’s t-test, categorical variables were compared using $\chi^2$-tests. Analysis of the primary endpoint variable was performed by the two-sided Wilcoxon-test, where patients were stratified according to beta-blocker treatment (this is identical to the van Elteren test). For visualization of
the distributions of the primary outcome in the two groups, a mirror histogram was constructed (Figure 2). Since these distribution 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 stratawise permutations and 95% bootstrap confidence intervals based on 10,000 repetitions. For time-to-event secondary outcome variables (parameter 1, 3, 4, and 9) Kaplan-Maier analyses including log-rank tests were performed, stratified by beta-blocker treatment. Additionally, stratified Cox proportional hazard models were fitted to the data in order to calculate hazard ratios and cumulative event rates for quantification and visualization of treatment effects. For the other secondary outcome variables (parameter 5, 6, 7 and 8) two-sided Wilcoxon-tests were performed, where patients were stratified according to beta blocker treatment analogue to the pre-specified analysis of the primary outcome. Quality of life data (SF-12 questionnaire, parameter 2) were analyzed using analysis of covariance (ANCOVA) with baseline adjustment. The probability of type I error was fixed to 5% two-sided and not adjusted for multiplicity of secondary endpoints. Instead, the secondary endpoints were hierarchically ordered as given above to allow an extension of a claim beyond the primary hypothesis (closed testing procedure) (14).

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 beta blocker strata. Second, for time-to-event endpoints, we checked the proportional hazards assumption by introducing a log(time) x treatment interaction as 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. And third, since the use of “recovery medication” may have diluted other treatment effects, a supportive analysis of the primary endpoint only consider-
ing patients without recovery medication was performed. Applied software: STATA Version 11.0, SAS for Windows, Version 9.2 (SAS Institute, Cary, NC, USA) and R (ver. 2.8).

Results

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

Tele-ECG recordings

A total of 97,159 tele-ECGs were recorded in the 425 patients during follow-up. 87,818 tele-ECGs (44,888 in the placebo group and 42,930 in the olmesartan group) could be used for analyses. 9,341 (9.6%) of the tele-ECGs did not fulfil quality criteria in the blinded analysis 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 endpoint

Figure 2 shows the distributions of the primary endpoint AF burden by treatment. Both distributions are very similar and reveal an essential bimodality with a marked mode at small AF burdens up to 10%, but above zero, and a smaller mode at AF burdens above 90%, resulting in an unexpectedly high standard deviation (pooled SD=0.262). The means were 14.7% in the placebo group and 15.1% in the olmesartan group and were neither significantly different in the pre-
specified analysis (p=0.770) nor in the sensitivity analysis (p=0.865) (Table 2). Due to the bi-modalitity of distributions, bootstrap confidence limits may be more reliable than t-test based confidence limits. The 95% confidence interval 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=0.022). Recovery medication was initiated in nine patients in the olmesartan group (4.2%) and 20 patients in the placebo group (9.5%). In any case, since the primary endpoint was not significant, no claim for an advantage of olmesartan in secondary outcomes can be derived from our data due to the pre-specified hierarchal 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 beta-blocker strata. The tendency to less prescriptions of amiodarone was only present if patients were on beta-blocker (no beta-blocker HR=1.09, 95% CI 0.15-7.73; beta-blocker HR=0.34, 95% CI 0.14-0.83, p=0.041). In the second post-hoc analysis, treatment x log(time) interactions were found for time to first occurrence of a documented relapse of atrial fibrillation (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 endpoints, survival curves were crossing with a significant trend towards 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 has favoured the placebo group in the primary analysis of AF burden. Thus, we performed a third post-hoc sensitivity analysis excluding the 29 patients who received a recovery medication during follow-up from the primary analysis. We found that patients with recovery medication on average had more AF burden (this may have been the reason for considering recovery medication) and, correspondingly, in a repetition of the primary analysis in the remaining 396 patients arithmetic means were lower (placebo 13.0%, olmesartan 14.7%, difference 0.017). However, the difference between groups remained non-significant (p=0.246), indicating that the differential use of recovery medication did not mask an olmesartan effect with respect to AF burden. In summary, use of recovery medication was rare and did not explain the lack of an effect of olmesartan on the primary outcome parameter.

**Serious Adverse Events**

65 serious adverse events (SAE) were reported by investigators and assessed by the blinded Critical Event committee. 41 of the events classified as non-serious while 24 of the events, which occurred in 21 patients, were classified as SAE according to ICH/GCP guidelines (Table 3). No significant differences were found between groups. There were three deaths in the trial. One 62-year old patient died in the placebo group due to a carcinoma of the pancreas. Two deaths occurred in the olmesartan group: one 69-year old patient died because of an assumed acute myocardial infarction in the course of heavy physical exercise after he had experienced significant dyspnoea and fatigue for some days. His LVEF at baseline was 56% without history
of coronary artery disease. The other patient was 74-year old when she died suddenly without preceding clinical symptoms. She had a diabetes mellitus type II and a moderately reduced LVEF at baseline without history of coronary artery disease. Other SAEs in the placebo group were one acute pancreatitis, two supraventricular tachycardia, and one acute myocardial infarction. Other SAEs in the olmesartan group were one episode of a non-sustained wide-QRS complex tachycardia (12 beats), one supraventricular tachycardia, one septic shock with acute respiratory distress syndrome, and one 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 to the placebo group.

Discussion

The ANTIPAF trial shows that the use of 40mg olmesartan in patients with paroxysmal AF is safe, but does not reduce the AF burden in comparison to placebo during one year follow-up. Furthermore, eight out of nine defined secondary outcome parameters like 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 beta-blocker prescriptions time to prescription of the recovery medication (amiodarone) tended to be shorter in the placebo group, the primary endpoint (AF burden) was still comparable in a subanalysis restricted to patients not receiving recovery medication (amiodarone). In any case, since the primary endpoint was not significant, no claim for an advantage of olmesartan in secondary outcomes can be derived from our data due to the pre-specified 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 (1-3,5,10). At the molecular level, angiotensin II, oxidative stress, and proinflammatory mediators are of particular importance to induce proarrhythmic structural remodelling and atrial ectopy in the area of the pulmonary veins (7-9,11,15,16). 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 (5,10,17-20). However, previous studies suggest that the concept to prevent structural atrial remodelling is more efficient for primary prevention of AF and 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 ARB and ACE-inhibitors in association with amiodarone to prevent AF (21,22,26). Of note, Madrid et al. found a dose-dependent effect of irbesartan on AF recurrence in 120 patients after cardioversion (27). However, these trials were relatively small and systematic ECG monitoring to detect silent AF was not used (21-23). In contrast, the GISSI-AF trial showed in more than 1400 patients with underlying cardiovascular diseases, diabetes mellitus, or left atrial enlargement no effect of ARB therapy on the recurrence of AF. However, the study did not exclude patients with ACE-inhibitor therapy (24). About 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 (AFL) and their influence on clinical outcomes in 42,418 hypertensive men and women >55 years of age with at least one additional cardiovascular risk factor. AF/AFL occurred in 641 participants (2.0%) and, excluding doxazosin, did not differ by antihypertensive treatment group (lisinopril, amlodipine, and thiazide-like diuretics) (28). Of note, in the high-risk hypertensive population, pre-existing and new-onset AF/AFL were associated with increased mortality. Similar to the ANTIPAF results, ALLHAT raises substantial questions regarding whether previous studies suggesting lower new-onset AF/AFL rates with ACE inhibitors or ARBs are generalizable. In accordance, the ACTIVE program and the ONTARGET study could also not show positive effects of ARBs on the occurrence of AF in patients with cardiovascular risk factors (25,29).

Nevertheless, meta-analyses still favour the use of ACE inhibitors and ARBs to reduce the occurrence of AF (5,10). A recent meta-analysis included a total of 23 randomized controlled trials with 87,048 patients (10). 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, RAS inhibition reduced the odds ratio for AF by 33%, but there was substantial heterogeneity among trials. In primary prevention, RAS inhibition was effective in patients with heart failure and those with hypertension and left ventricular hypertrophy but not in post-myocardial infarction patients overall. In secondary prevention, RAS inhibition was often 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.

Based on existing data, it remained to be determined if 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 may often depend on ectopic activity mostly originating from the pulmonary veins. This was tested in the ANTIPAF trial, which was 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. Since 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 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 any type of recurrence independent of symptoms was counted in the primary endpoint. During one year of 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 profibrillatory 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 remodelling 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 inadequate dosage of olmesartan since 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 the very high variability of AF recurrences in patients with paroxysmal AF. Thus, it appears very unlikely that non-systematic and intermittent ECGs or Holter recordings can assess the true burden of AF. This should be considered in future attempts to assess the efficacy of pharmacological and non-pharmacological antiarrhythmic approaches. The only parameter, which was found to be different in the two study groups was the time to prescription of the recovery medication (amiodarone), which was given earlier and more frequent in the placebo group. This is consistent with the observation that patients with recovery medication, on average, had more AF burden. However, AF burden in the two 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 felt to be unethical to compare ARB therapy with placebo in symptomatic AF patients over an extended time 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 to 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 ARBs or ACE inhibitors in AF patients without concomitant structural heart disease. These findings have influenced the 2010 ESC AF-guidelines (30). The ESC guidelines 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.

**Limitation**

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/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 times periods (>1 year) with implanted devices and analyses of very large patient populations might be the only way to determine mild or modest differences between paroxysmal AF patients. 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 different trends that suggest possible differences beyond the time interval studied (Figure 3).

**Conclusion**

ARB therapy per se does not reduce the number of AF episodes in patients with documented paroxysmal AF without structural heart disease during one year follow-up. Therefore, ARBs may not be recommended as first line treatment in this clinical setting if not indicated for other reasons.
Acknowledgments: All participating centres and participating physicians were located in Germany and are listed in a supplementary file.

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Conflict of Interest Disclosures: A.G. has received speaker fees from Daiichi-Sankyo Deutschland GmbH.

References:


Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Placebo (N=211)</th>
<th>Olmesartan (N=214)</th>
<th>p-value</th>
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<td>Age (years)</td>
<td>61.9±10.2</td>
<td>61.1±11.2</td>
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<tr>
<td>Women – no. (%)</td>
<td>95 (45.0)</td>
<td>81 (37.9)</td>
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<td>Arterial hypertension – no. (%)</td>
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<td>106 (49.5)</td>
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<td>Diabetes mellitus– no. (%)</td>
<td>18 (8.5)</td>
<td>17 (7.9)</td>
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<td>Hx of smoking – no. (%)</td>
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<td>91 (42.5)</td>
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<td>Coronary artery disease– no./total no. (%)</td>
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<td>11/205 (5.4)</td>
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<td>197/212 (92.9)</td>
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<td></td>
<td>Class I 8/211 (3.8)</td>
<td>6/212 (2.8)</td>
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<td>Class II 6/211 (2.8)</td>
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<td></td>
<td>Class III 1/211 (0.5)</td>
<td>0/212 (0.0)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Class IV 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 – no./total no. (%)</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>BUN (mg/dl)</td>
<td>31.0±17.4</td>
<td>32.8±16.0</td>
<td>0.259</td>
</tr>
<tr>
<td>Medication – no./total no. (%)</td>
<td>Beta-blocker (stratum) 149/211 (70.6)</td>
<td>152/214 (71.0)</td>
<td>0.926</td>
</tr>
<tr>
<td></td>
<td>Dihydropyridines 23/162 (14.2)</td>
<td>23/170 (13.5)</td>
<td>0.860</td>
</tr>
<tr>
<td></td>
<td>Diltiazem 1/162 (0.6)</td>
<td>1/170 (0.6)</td>
<td>0.973</td>
</tr>
<tr>
<td></td>
<td>Class IV antiarrhythmic agent 6/162 (3.7)</td>
<td>8/170 (4.7)</td>
<td>0.649</td>
</tr>
<tr>
<td></td>
<td>Verapamil 5/162 (3.1)</td>
<td>7/170 (4.1)</td>
<td>0.614</td>
</tr>
<tr>
<td></td>
<td>Ca antagonist 29/162 (17.9)</td>
<td>30/170 (17.7)</td>
<td>0.952</td>
</tr>
<tr>
<td></td>
<td>Diuretics 24/162 (14.8)</td>
<td>22/170 (12.9)</td>
<td>0.621</td>
</tr>
<tr>
<td></td>
<td>Nitrates 3/162 (1.9)</td>
<td>2/170 (1.2)</td>
<td>0.613</td>
</tr>
<tr>
<td></td>
<td>Statins 25/162 (15.4)</td>
<td>16/170 (9.4)</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>ASS 48/162 (29.6)</td>
<td>53/170 (30.6)</td>
<td>0.849</td>
</tr>
<tr>
<td></td>
<td>OAC 46/162 (28.4)</td>
<td>36/170 (30.6)</td>
<td>0.127</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>64.3±11.8</td>
<td>64.0±12.6</td>
<td>0.749</td>
</tr>
<tr>
<td>Systolic RR (mmHg)</td>
<td>132.5±18.7</td>
<td>130.0±18.3</td>
<td>0.210</td>
</tr>
<tr>
<td>Diastolic RR(mmHg)</td>
<td>79.9±10.2</td>
<td>78.2±8.6</td>
<td>0.098</td>
</tr>
<tr>
<td>CHADS2 score*</td>
<td>0.5 (0-4), 0.7 (0.9)</td>
<td>0 (0-4), 0.7 (0.9)</td>
<td>0.9016</td>
</tr>
<tr>
<td>CHA2DS2-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>

Plus-minus values are means ± SD. T-test for continuous variables, Pearson Chi-square test with continuity correction for categorical variables; Hx= history of; NYHA=New York Heart Association Class; BUN=blood urea nitrogen; ASS=aspirin; OAC=oral anticoagulants
*For CHA2DS2-Vasc and CHADS2 scores median (range), mean (SD) are given. Groups were compared using Wilcoxon-Mann-Whitney test.
### Table 2: Primary endpoint and secondary outcome parameters

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Description</th>
<th>Placebo</th>
<th>Olmesartan</th>
<th>Olmesartan vs. Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (95% CI)</td>
<td>Mean (95% CI)</td>
<td>Difference</td>
<td>p-value</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Percentage of days of atrial fibrillation</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>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td></td>
<td>Percentage of days of atrial fibrillation after a treatment wash-in phase of 90 days†</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>
</tr>
<tr>
<td><strong>Secondary Endpoints</strong></td>
<td>Number of hospitalizations for cardiovascular reasons according to endpoint 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>
</tr>
<tr>
<td></td>
<td>Number of intermediate medical visits without hospitalization for cardiovascular reasons according to endpoint 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>
</tr>
<tr>
<td></td>
<td>Number of 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>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td><strong>Cumulative Event rate at 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td><strong>Event Information</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Time to first occurrence of a documented relapse of atrial fibrillation‡</td>
<td>78.5%</td>
<td>76.8%</td>
<td>1.031 (0.828 to 1.283)</td>
<td>0.786#</td>
</tr>
<tr>
<td></td>
<td>Time to persistent atrial fibrillation‡</td>
<td>9.0%</td>
<td>9.2%</td>
<td>1.080 (0.571 to 2.042)</td>
<td>0.812#</td>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td></td>
<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>
</tr>
</tbody>
</table>

† Stratum 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 logrank test
Table 3: Serious adverse events by study group in the safety set

<table>
<thead>
<tr>
<th>Type of adjudicated SAE</th>
<th>Placebo (n=215) Number of patients (percentage)</th>
<th>Olmesartan (n=215) Number of patients (percentage)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute heart failure</td>
<td>1 (0.47%)</td>
<td>1 (0.47%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (0.47%)*</td>
<td>1 (0.47%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>0 (0%)</td>
<td>1 (0.47%)</td>
<td>0.317</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.47%)</td>
<td>2 (0.93%)</td>
<td>0.562</td>
</tr>
<tr>
<td>Cerebrovascular complications</td>
<td>2 (0.93%)</td>
<td>1 (0.47%)</td>
<td>0.562</td>
</tr>
<tr>
<td>Syncope</td>
<td>2 (0.93%)</td>
<td>0 (0%)</td>
<td>0.156</td>
</tr>
<tr>
<td>Other</td>
<td>4 (1.86%)</td>
<td>4 (1.86%)*</td>
<td>1.000</td>
</tr>
<tr>
<td>Any SAE</td>
<td>11 (5.12%)</td>
<td>10 (4.65%)</td>
<td>0.823</td>
</tr>
</tbody>
</table>

* one patient had three events
† one patient had two events

Figure Legends:

Figure 1: Trial profile. Patients were stratified by β-blocker use before randomization. PAF = paroxysmal atrial fibrillation, SR = sinus rhythm, ITT=intention-to-treat.

Figure 2: Distribution of the primary study endpoint (AF burden) by study group. For visualization, a mirror histogram of the distribution of the primary endpoint in the two comparison groups is shown (p=0.770).

Figure 3: Cumulative incidence rates of AF recurrence by study group showed no difference between treatment groups (p(hazard ratio)=0.786). In the second post-hoc analysis, treatment x log(time) interactions were found for time to first occurrence of a documented relapse of atrial fibrillation (p(trend differences)=0.004).
467 participants assessed for eligibility

37 participants excluded because of:
- improper inclusion criteria (36) or
- missing informed consent (3)

**Inclusion**

430 patients with documented PAF and SR (≤ 6 months)
(Age ≥ 18 years)

**Stratification**

- Concomitant β-blocker therapy

**Stratum A**

Randomization 1:1

- **Group 1**
  - Placebo
  - n = 211 (ITT-population)
    - 4 pts. withdrawn because no tele-ECG was recorded

- **Group 2**
  - 40 mg Olmesartan
  - n = 214 (ITT-population)
    - 1 pt. withdrawn because no tele-ECG was recorded

**Stratum B**

Randomization 1:1

**Stratification**

Yes

No