Absence of protective effect of renin-angiotensin system inhibitors on atrial fibrillation development: Insights from the Canadian Trial of Atrial Fibrillation (CTAF)

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M Palardy, A Ducharme, S Nattel, et al; on behalf of the CTAF Investigators. Absence of protective effect of renin-angiotensin system inhibitors on atrial fibrillation development: Insights from the Canadian Trial of Atrial Fibrillation (CTAF). *Can J Cardiol* 2008;24(9):709-713.

BACKGROUND: Antiarrhythmic agents have modest efficacy in preventing atrial fibrillation (AF) recurrence. Although retrospective analyses have suggested a preventive effect of inhibitors of the renin-angiotensin system (RAS) on AF development in patients with congestive heart failure or hypertension, the value of these agents has not been evaluated in patients with AF but without a high prevalence of hypertension or heart failure.

METHODS AND RESULTS: A retrospective analysis of the Canadian Trial of Atrial Fibrillation (CTAF) was conducted. CTAF demonstrated the superiority of amiodarone (A) over sotalol or propafenone (SP) in maintaining sinus rhythm in patients with AF. Of the 403 patients randomly assigned in CTAF, 11.7% of the A group and 12.7% of the SP group were receiving a RAS inhibitor at baseline. By multivariate analysis (including all the risk factors known to be associated with AF available in the database), the use of RAS blockers in addition to antiarrhythmic agents was not associated with additional benefit against AF development. There was a recurrence of AF in 59 patients (38.3%) and 14 patients (29.8%) of groups A and A-RAS, respectively, while 93 patients (61.6%) and 32 patients (62.8%) of the SP and SP-RAS groups, respectively, experienced recurrent AF.

CONCLUSION: Blocking the RAS did not provide additional benefit against AF recurrence in CTAF patients treated with an antiarrhythmic drug. These results underscore the need for randomized clinical trials to clearly define the role of RAS inhibitors in treating AF.

Key Words: Angiotensin; Angiotensin-converting enzyme inhibitors; Angiotensin receptor blockers; Atrial fibrillation; CTAF

Atrial fibrillation (AF) is the most frequent sustained arrhythmia encountered in clinical practice (1); it can lead to cardiac decompensation and stroke, with increased morbidity and mortality. Key risk factors contributing to AF development include older age, hypertension, diabetes, chronic heart failure (CHF), valvular heart disease, myocardial infarction (MI) and left atrial size (2-5). In patients with AF, maintenance of sinus rhythm with antiarrhythmic agents remains challenging, with nearly 50% recurrence at six months (6) and potential drug-induced proarrhythmias. A recent analysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial suggested that sinus rhythm was

L'absence d'effet protecteur des inhibiteurs du système rénine-angiotensine sur le développement de la fibrillation auriculaire : Aperçu de l'essai canadien CTAF sur la fibrillation auriculaire

HISTORIQUE : L'efficacité des antiarythmiques à prévenir la récurrence de la fibrillation auriculaire (FA) est modeste. Même si les analyses rétrospectives laissent supposer un effet préventif des inhibiteurs du système rénine-angiotensine (SRA) sur le développement de la FA chez les patients atteints d'insuffisance cardiaque congestive ou d'hypertension, la valeur de ces agents n'a fait l'objet d'aucune évaluation chez les patients atteints de FA sans prévalence élevée d'hypertension ou d'insuffisance cardiaque.

MÉTHODOLOGIE ET RÉSULTATS : Les auteurs ont procédé à une analyse rétrospective de l'essai canadien CTAF sur la fibrillation auriculaire. L'essai CTAF a démontré la supériorité de l'amiodarone (A) sur le sotalol ou la propafénone (SP) pour maintenir le rythme sinusal chez les patients atteints de FA. Sur les 403 patients sélectionnés au hasard pour l'essai CTAF, 11,7 % de ceux du groupe A et 12,7 % de ceux du groupe SP ont reçu un inhibiteur du SRA au départ. Par analyse multivariée (y compris tous les facteurs de risque associés à la FA disponibles dans la base de données), l'utilisation des inhibiteurs du SRA en plus des antiarythmiques n'apportait pas d'avantages supplémentaires contre le développement de la FA. Les auteurs ont observé une FA récurrente chez 59 patients (38,3 %) et 14 patients (29,8 %) des groupes A et A-SRA, respectivement, tandis que 93 (61,6 %) et 32 patients (62,8 %) des groupes SP et SP-SRA, respectivement, ont présenté une FA récurrente.

CONCLUSION : Le fait d'inhiber le SRA n'apportait pas d'avantages supplémentaires contre la récurrence de FA chez les patients de l'essai CTAF traités par antiarythmique. Les résultats soulignent la nécessité de mener des essais aléatoires et contrôlés pour définir clairement le rôle des inhibiteurs du SRA dans le traitement de la FA.

associated with improved survival, but this effort may be offset by the negative effects of antiarrhythmic drugs (7). Thus, new approaches to the prevention of AF are needed, and the so-called upstream method, tackling the problem earlier on in its natural history, may be appealing.

In persistent AF, natriuretic peptides (8) and aldosterone (9) serum levels are elevated, but decrease after electrical cardioversion (10), suggesting increased neurohumoral activity, including the renin-angiotensin system (RAS). In addition to neurohumoral activation, the knowledge that 'AF begets AF' (11) is well recognized and has led to the description of two remodelling processes (12). First, the

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Received for publication October 31, 2007. Accepted January 28, 2008

concept of electrical remodelling implies alterations of atrial electrophysiological properties, including changes in ionic currents, resulting in partial loss of the normal physiological rate adaptation and shortening of the effective refractory period (13-17). Second, profound atrial structural changes, including dilation and interstitial fibrosis, may be found in AF, particularly when associated with CHF; these changes are at least partially induced by activation of the RAS (18).

Both clinical and experimental studies in subjects with left ventricular (LV) systolic dysfunction, symptomatic CHF regardless of LV ejection fraction (LVEF) (10,19-22) and hypertension with LV hypertrophy (LVH) (23) have demonstrated a reduction in AF incidence using RAS inhibitors. However, it is less clear whether these agents have a beneficial effect on AF development in patients without CHF or LVH, in which the hemodynamic effects of RAS inhibition and structural remodelling may be more modest. The Canadian Trial of Atrial Fibrillation (CTAF) (24) demonstrated that amiodarone is superior to propafenone or sotalol in maintaining sinus rhythm in patients with AF. We evaluated the impact of RAS inhibitors on the recurrence of AF in the CTAF population.

METHODS

Patient population

CTAF (24) was a prospective randomized multicentre study that included 403 patients (201 in the amiodarone group and 202 in the sotalol/propafenone group). Patients with an episode of electrocardiogram (ECG)-documented sustained symptomatic AF (longer than 10 min) in the preceding six months were studied. Patients were excluded if they had long-lasting AF (longer than six months), reversible etiologies of AF, recent MI (six months or less), cardiac surgery (30 days or less), New York Heart Association class III or IV, and renal dysfunction (250 $\mu\text{mol/L}$). The primary end point was the time to first recurrence of AF. The main results have been published and showed the superiority of amiodarone over sotalol/propafenone.

Statistical analysis

For the purpose of the present analysis, the study population was divided into four groups according to treatment arm and RAS inhibitor use. The time to first episode of AF recurrence was analyzed using the Kaplan-Meier method and differences between the four groups (amiodarone with or without a RAS inhibitor, and sotalol/propafenone with or without a RAS inhibitor) were assessed using the log-rank test. For this analysis, follow-up started on day 21 after random assignment, providing time for amiodarone loading, other medication adjustment and electrical cardioversion, as needed. The Cox regression model was used to calculate RR and to investigate potential differences among subgroups (RAS inhibitor use, random assignment to amiodarone, hypertension, LV dysfunction, age and diabetes). Statistical analysis was performed using SAS version 8.2 (SAS Institute, USA), based on the intention-to-treat principle, with a significance level of 5%.

To limit the effects of independent nominal confounding variables, χ^2 values were also calculated. ANOVA was applied to compare baseline variables, such as age and heart rate, between the four groups. Univariate and multivariate analysis models were performed to calculate the hazard ratios of the independent variables on the occurrence of the primary end point, including the same variables.

Data are expressed as mean $\pm$ SD for continuous variables and as percentages for categorical variables. Baseline characteristics were analyzed for statistical differences between the four groups. Data were censored if the patient died or reached the end of the follow-up period, or was lost to follow-up without a documented AF occurrence.

RESULTS

Results are presented for the four patient groups as follows: patients randomly assigned to amiodarone without RAS inhibitor therapy (A),

patients randomly assigned to amiodarone with RAS inhibitor therapy (A-RAS), patients randomly assigned to sotalol/propafenone without RAS inhibitor therapy (SP) and patients randomly assigned to sotalol/propafenone with RAS inhibitor therapy (SP-RAS).

Baseline characteristics

At baseline, 98 patients (24.3%) of the CTAF population were receiving a RAS inhibitor, divided evenly between the A and SP groups (Table 1). Only 12% of patients included in the whole study had some degree of LV dysfunction (LVEF lower than 50%), and despite 46% of patients having a history of hypertension, only 17% had LVH on the baseline ECG. Patients taking RAS inhibitors were older and had a higher incidence of hypertension, but the incidence of diabetes, LVH and LV systolic dysfunction (LVEF lower than 50%) was not significantly different between groups. There was an increased use of diuretics among RAS-treated patients (41.8% versus 15.4%). In addition, patients on RAS inhibitors had a higher frequency of persistent AF at baseline, as well as a higher frequency of AF longer than one week in duration, and more patients in the SP-RAS group were in AF on the baseline ECG (51%) compared with the other groups.

Deaths and loss to follow-up: Ten patients were lost to follow-up; nine deaths occurred in the A group (five in A and four in A-RAS) and eight deaths occurred in the SP group (five in SP and three in SP-RAS) (P not significant for all).

Recurrence of AF

The mean follow-up was 468 ± 150 days. Fourteen patients (29.8%) in A-RAS experienced AF recurrence without any beneficial effects of RAS inhibitors compared with 59 in A (38.3%), and 32 patients in SP-RAS (62.8%) experienced AF recurrence without any beneficial effects of RAS inhibitors compared with 93 in SP (61.6%) (Figure 1), even among patients in sinus rhythm after cardioversion.

Further analysis for AF recurrence between the A and SP groups, after adjustment for RAS inhibitor use, did not suggest any significant benefits of RAS antagonists. Both univariate and multivariate analyses failed to demonstrate any protective effects of RAS inhibitor use (Figure 2 and Table 2).

To further appreciate the potential protective effects of RAS inhibition, an exploratory analysis was performed, which included only patients with a history of hypertension (184 of 403 patients [46% of the cohort]). Amiodarone had the same preventive impact on sinus rhythm maintenance in this subgroup of patients (Figure 3) without any incremental effects of RAS inhibitor use.

DISCUSSION

In the present retrospective analysis of CTAF, inhibition of angiotensin II activity did not lead to additional benefits on AF recurrence, even when the analysis was restricted to hypertensive patients. There are several potential explanations for this observed lack of effect: the overall characteristics of the patient population enrolled in CTAF, the differences in clinical characteristics of patients treated with RAS inhibition, or the type of AF necessary to obtain an intrinsic antiarrhythmic effect with RAS inhibitors.

First, important differences in patient populations between the previously published data, and our study may, at least partly, explain the apparent discrepancy. The protective effect of RAS inhibition has been demonstrated in patients with impaired LVEF (20,22), early post-MI (25), symptomatic CHF regardless of LVEF (19) or hypertension with LVH (23). In contrast, CTAF enrolled very few patients with these conditions and excluded severely symptomatic CHF patients (New York Heart Association class III or IV). In the high-risk situations of CHF (12) or LVH, the increase in angiotensin II levels and its tissue effects through the mitogen-activated protein kinase system may cause atrial structural remodelling, including loss of myocytes, disorganization of the sarcoplasmic reticulum and

TABLE 1
Baseline characteristics of patient subgroups

	A (n=154)	A-RAS (n=47)	SP (n=151)	SP-RAS (n=51)	P*
Age (years)	64±11	69±9	64±11	69±8	0.0006
Male sex	59.1	40.4	58.3	49.0	0.09
BP, systolic (mmHg)	138±19	149±24	131±19	141±23	<0.0001
BP, diastolic (mmHg)	78±11	81±11	77±13	79±12	0.24
Heart rate (beats/min)	74.6±24	77.6±25	77.4±24	83.5±29	0.17
New York Heart Association functional class					0.25
I	72.7	57.5	68.5	60.8	
II	24.7	40.4	30.1	39.2	
III	2.6	2.1	1.4	0	
Medical history					
History of MI†	19.0		18.0		0.68
Valvular disease‡	12.3	19.2	12.6	13.7	0.66
Hypertension	31.8	83.0	35.1	84.3	<0.0001
Diabetes	6.5	19.2	11.3	7.8	0.07
History of atrial fibrillation					
Paroxysmal	51.3	40.4	47.7	29.4	0.04§
Persistent	48.7	59.6	52.3	70.6	
Duration of atrial fibrillation at baseline					0.46
<24 h	54.0	40.6	44.3	41.7	
>24 h – 7 days	16.8	9.4	19.5	8.3	
>7 days	27.4	46.9	31.0	47.2	
Electrical cardioversion	19.5	19.2	25.2	23.5	0.63
Rhythm on electrocardiogram					
Sinus	62.8	63.8	65.6	49.0	0.21
Atrial fibrillation	34.0	36.2	33.1	51.0	0.12
Atrial flutter	0.7	0	0.7	3.9	0.15
Paced	1.3	4.3	2.0	0	0.41
Other	0	0	0.7	0	0.64
Echocardiography					
LA dimension (mm)	40.9±6.8	41.8±6.1	40.5±6.8	41.9±6.2	0.48
LVEF <50%	9.2	19.2	10.2	18.0	0.13
LV hypertrophy	11.7	17.0	21.6	18.0	0.15
Medication					
Digoxin	33.1	38.3	29.1	45.1	0.18
Beta-blocker	31.2	23.4	26.5	31.4	0.65
Calcium channel blocker	23.4	17.0	29.1	25.5	0.36
Diuretic	15.6	46.8	15.2	37.3	<0.0001
Acetylsalicylic acid	22.1	25.5	27.2	27.5	0.74
Warfarin†	58.0		57.0		NA
Lipid-lowering agent	13.0	12.8	8.6	17.7	0.34
Thyroid hormone supplement	9.7	10.6	8.0	5.9	0.79

Data are expressed as mean ± SD for continuous variables and percentages for categorical variables. *P measured for difference between the four groups; †Data of subgroups unavailable (data from original article); ‡Hemodynamically significant; §P combined for paroxysmal and persistent atrial fibrillation. A Amiodarone group not receiving renin-angiotensin system (RAS) inhibitor therapy; A-RAS Amiodarone group receiving RAS inhibitor therapy; BP Blood pressure; LA Left atrial; LV Left ventricular; LVEF Left ventricular ejection fraction; MI Myocardial infarction; NA Not available; SP Sotalol/propafenone group not receiving RAS inhibitor therapy; SP-RAS Sotalol/propafenone group receiving RAS inhibitor therapy

inflammatory changes (26), which, together, may create the fibrotic substrate for intra-atrial re-entry. These changes, associated with higher filling pressure and atrial stretch, may induce local conduction abnormalities (27), rendering the left atrium vulnerable to further AF development (28,29). In patients who have no associated CHF or

Figure 1) Kaplan-Meier event-free survival curves for atrial fibrillation recurrence based on subgroup. A statistically significant difference ($P<0.0001$) was found only between amiodarone (A and A-RAS) and sotalol/propafenone (SP and SP-RAS) allocation, whereas no statistical significance could be demonstrated when subdividing by RAS inhibitor use subgroups ($P=0.30$ and $P=0.96$, respectively, for the amiodarone [A versus A-RAS] and the sotalol/propafenone [SP versus SP-RAS] groups). A Amiodarone group not receiving renin-angiotensin system (RAS) inhibitor therapy; A-RAS A Amiodarone group receiving RAS inhibitor therapy; S Sotalol/propafenone group not receiving RAS inhibitor therapy; SP-RAS Sotalol/propafenone group receiving RAS inhibitor therapy

Figure 2) Hazard ratios and the 95% CI for each variable included in the multivariate model. Amiodarone was the only variable found to have a significant protective effect on atrial fibrillation recurrence. LVEF Left ventricular ejection fraction; RAS Renin-angiotensin system

TABLE 2
Hazard ratios for the recurrence of atrial fibrillation: Univariate analysis

Variable	Hazard ratio	95% hazard ratio CI
Renin-angiotensin system inhibitor	0.920	0.661–1.280
Amiodarone	0.456	0.341–0.610
Diabetes	0.866	0.527–1.424
Age	0.991	0.979–1.004
Hypertension	1.022	0.773–1.352
Left ventricular ejection fraction	0.979	0.628–1.526

Model of univariate analysis with hazard ratios and the associated 95% CI expressed for each variable studied. The only parameter found to be statistically significant was amiodarone

Figure 3) Kaplan-Meier event-free survival curves for atrial fibrillation recurrence based on history of hypertension. A statistically significant difference ($P < 0.0001$) was observed between amiodarone (A and A-RAS) and sotalol/propafenone (SP and SP-RAS), whereas no statistical significance could be demonstrated when subdividing by renin-angiotensin system (RAS) inhibitor use subgroups ($P = 0.31$ and $P = 0.56$, respectively, for the amiodarone [A versus A-RAS] and the sotalol/propafenone [SP versus SP-RAS] groups). A Amiodarone group not receiving renin-angiotensin system (RAS) inhibitor therapy; A-RAS A Amiodarone group receiving RAS inhibitor therapy; S Sotalol/propafenone group not receiving RAS inhibitor therapy; SP-RAS Sotalol/propafenone group receiving RAS inhibitor therapy

LVH, changes in electrical and structural remodelling induced by AF may be more modest and, consequently, therapy with RAS inhibitor may be less effective. Our results are concordant with a post hoc analysis of AFFIRM (5). However, our results seem to be in contradiction with a small, open-label study from Hong Kong (30) comparing amiodarone alone or in combination with losartan or perindopril for the prevention of AF recurrence in patients with lone paroxysmal AF. Both agents were effective for symptomatic AF prevention, but not for documented asymptomatic AF. Although interesting, this trial cannot provide a definitive answer due to this symptom discrepancy and the lack of information about the actual percentage of patients in AF at random assignment.

On the other hand, patients in CTAF who were receiving RAS inhibitors were older, more frequently hypertensive and had more persistent AF than those who were not treated with RAS inhibitors. However, the incidence of AF recurrence between the two groups was the same, which may suggest that RAS blockade had a beneficial effect in the high-risk group.

In addition to different patient populations, the importance of electrical remodelling and drug therapy at baseline could also have played a role (15). While rapid atrial pacing shortens the atrial effective refractory period, increases AF duration (11) and may cause atrial cardiomyopathy (31), these changes could be attenuated with the use of RAS antagonists experimentally (21) and in patients with persistent AF (mean of six months) undergoing electrical cardioversion

(32). AF duration is a known major determinant of AF recurrence and electrical remodelling (14), and only 35% of the CTAF patients had AF longer than seven days. In addition, the use of beta-blockers and calcium channel blockers has been shown to exert some protective effects on AF recurrence (5,14,17,33), probably through prevention of ionic remodelling (13,14,34) and reduced endogenous angiotensin II production; their use was three times higher in CTAF than in these previous trials (33% compared with 11%). Thus, greater use of these agents could minimize the overall clinical benefits of RAS inhibitor use. Furthermore, CTAF patients were more often treated with diuretics (22% versus 5%), which may influence atrial preload, stretch and wall stress, hence decreasing triggers of AF development (34).

Last, it is also possible that RAS inhibitors have no antiarrhythmic properties per se. This seems unlikely, given the results of two recent meta-analyses (35,36) confirming their protective effect on incidence of AF. However, in the analysis by Healey et al (36), the efficacy was limited to patients with heart failure or hypertension with LVH.

Our results highlight the fact that additional prospective, randomized double-blind studies are needed to confirm the beneficial actions of RAS inhibition and to delineate the patient subgroups that will benefit. At least three ongoing randomized trials have identified AF development as a predefined secondary end point. They should help to better understand the role of RAS antagonists in AF prevention.

Limitations

The limitations of our analysis are mainly related to its retrospective nature. First, patients receiving RAS inhibitors differed clinically from those who were not receiving RAS inhibitors. Although we tried to limit bias by adjusting for the impacts of possible risk or protective factors in the overall CTAF population with multiple factor analysis, it is possible that we were not able to fully control for other confounders. Second, data on RAS inhibitor dose and its adjustment over the course of the study were not available, and it is possible that patients received less-than-optimal dosages of these agents. Last, the CTAF study population was small, with a relatively short follow-up, and the favourable trend seen in the A-RAS group could represent a real effect that did not reach significance because of insufficient statistical power. Nevertheless, our data suggest that the protective effects of antagonists of the RAS on AF development may be dependent on the type of populations studied and their global cardiovascular risk factors.

CONCLUSION

The present retrospective analysis of CTAF was unable to demonstrate any significant benefits of the use of RAS inhibitors on AF recurrence. A potential explanation for this absence of effects may be that RAS inhibitors' preventive effect on AF occurrence depends on the level of individual cardiovascular risks, with CHF and complicated hypertensive patients gaining the most from this treatment. The present study highlights the need for prospective randomized trials to delineate the subgroups that will benefit.

ACKNOWLEDGEMENTS AND FUNDING: Drs Ducharme and White are supported by the Fonds de la recherche en santé du Québec. Dr Tardif holds a Pfizer and Canadian Institutes of Health Research chair.

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