



Canadian Cardiovascular Congress

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Landmark Trial Reinvigorates Treatment Options for Patients with Atrial Fibrillation

Toronto - In Canada, no new antiarrhythmic strategies have emerged over the past 20 years for the treatment of atrial fibrillation (AF), leaving a large unmet need for tremendous numbers of patients. This is especially true for those with concomitant AF and heart failure, whose prognosis is much worse than those without heart failure whether or not they have poor or preserved systolic function, and for whom treatment options are extremely limited. Indeed, findings from the AF-CHF trial failed to demonstrate that restoring and maintaining sinus rhythm in patients with AF and heart failure reduced cardiovascular (CV) mortality more effectively than a rate-control strategy, and more patients in the rhythm-control arm required hospitalization than in the rate-control group. Consequently, ATHENA study findings are highly intriguing, as for the first time, hard clinical end points—including CV mortality, arrhythmic death and stroke—were all significantly lower in patients who received dronedarone, a new multi-channel antiarrhythmic agent, compared with placebo, with no excess risk of serious adverse events seen with active therapy. After 20 years, Canadian physicians can expect this investigational agent to significantly ameliorate their treatment of AF patients, offering them a chance to improve not only symptoms and quality of life, but prognosis as well.

Toronto – Au Canada, aucune nouvelle stratégie antiarythmique n'a vu le jour depuis 20 ans dans le traitement de la fibrillation auriculaire (FA), de sorte que les besoins d'un grand nombre de patients demeurent insatisfaits. Cela est particulièrement vrai pour les insuffisants cardiaques présentant une FA, dont le pronostic est nettement plus sombre qu'en l'absence d'insuffisance cardiaque (IC), que la fonction systolique soit préservée ou non. Le nombre d'options de traitement dont on dispose pour ces patients est extrêmement limité. L'essai AF-CHF n'a pas réussi à démontrer que la restauration et le maintien du rythme sinusal en présence de FA et d'IC permettaient de réduire la mortalité d'origine cardiovasculaire (CV) de façon plus marquée qu'une stratégie visant à ralentir la fréquence cardiaque; en outre, l'hospitalisation a été nécessaire chez un plus grand nombre de patients du groupe «contrôle du rythme» que de patients du groupe «contrôle de la fréquence». Les résultats de l'étude ATHENA sont donc très intrigants car, pour la première fois, les taux de mortalité CV, de mortalité pour cause d'arythmie et d'AVC – les paramètres majeurs – ont tous été significativement plus faibles chez les patients sous dronedarone, nouvel antiarythmique inhibant de multiples canaux ioniques, que chez les témoins sous placebo, et le traitement actif n'a pas majoré le risque d'effet indésirable grave. Après 20 ans d'attente, les médecins du Canada peuvent maintenant aspirer non seulement à une amélioration des symptômes et de la qualité de vie du patient dans le traitement de la FA, mais aussi à un meilleur pronostic.

By Pam Harrison

The biggest problem with atrial fibrillation (AF)—the most common arrhythmia in clinical practice today and one that is increasing in prevalence—is stroke. Approximately one-quarter of strokes among the elderly are caused by AF, as pointed out by Dr. Malcolm Arnold, Professor of Medicine, Physiology and Pharmacology, University of Western Ontario, London. While warfarin can significantly reduce stroke risk (ASA less so), major bleeding is still a real concern with any anticoagulant therapy—“so the risks associated with AF are not only due to the arrhythmia itself but what we do to our patients with AF as well,” he added.

AF may emerge along the spectrum of cardiovascular disease (CVD) but it is especially prevalent in the hypertensive population. In the LIFE study, for example, rates of all-cause mortality, CV death, sudden cardiac death and stroke were significantly higher in hypertensive patients with AF than those without AF. Similarly, 20% of heart failure patients in one study also developed AF over a four-year follow-up, increasing mortality risk in both men and women. AF also occurs in many patients with heart failure with both reduced and preserved ejection fractions (EFs), as Dr. Arnold noted: regardless of whether EF is poor or preserved, mortality rates are similar in the two patient groups.

Dr. Paul Dorian, Professor of Medicine, University of Toronto, in turn, argued that “ECG-focused” outcome measures, including time to first recurrence of AF and AF burden, are not clinically meaningful for patients with AF. Instead, he advocated that physicians use “patient-centred” outcomes to meaningfully assess the value of any new

antiarrhythmic agent, including symptoms and how it makes patients feel. Equally important, studies may report adverse events as part of their overall findings but not as a prespecified end point—an oversight, as Dr. Dorian remarked, as any treatment that makes patients feel worse than the condition being treated cannot be considered very effective.

He also reminded delegates that many episodes of AF are not symptomatic and even when they are, many are minimally symptomatic. “Thus, measuring AF burden does not give a true reflection of the extent of disability or quality-of-life impairment or stroke risk related to the rhythm disorder,” he told delegates.

Indeed, stroke risk is determined by a patient's CHAD score—i.e. congestive heart failure, hypertension (or treated hypertension), age >75 years, diabetes—not the amount of AF that may be present. Nor does the presence or absence of AF help physicians make decisions about antithrombotic therapy, as he observed.

“Measuring therapeutic outcomes in patients with AF should be primarily related to symptoms, patient well-being and quality of life,” Dr. Dorian reiterated, “and hard outcomes such as heart failure episodes, hospitalizations and death, rather than counting the number of AF episodes... will lead to a more clinically relevant assessment of the effectiveness of therapies for AF.”

AF-CHF, ATHENA Trials

The question as to whether patients with AF should be cardioverted or treated to achieve adequate rate control has long

been debated, especially in patients with concurrent heart failure. To that end, The Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial was designed to test whether restoring and maintaining sinus rhythm—largely through the use of amiodarone—would reduce CV mortality compared with a rate-control strategy in AF patients with heart failure.

As discussed by Dr. Denis Roy, Professor of Medicine, Université de Montréal, Quebec, 682 patients were randomized to rhythm control while 694 were assigned to rate control. Most were in NYHA class III-IV with a mean EF of 27%. At a median follow-up of 37 months, mortality rates at approximately 27% for each treatment arm were virtually identical, while hospitalization rates at 46% were slightly higher in the rhythm control arm than the rate-control arm at 39%. “Our results suggest that rate control should be considered a primary approach for patients with AF and heart failure,” Dr. Roy concluded, adding that currently, amiodarone is the only option physicians really have available for the treatment of AF in the setting of heart failure.

Given the suboptimal efficacy of antiarrhythmic agents by rhythm control to reduce stroke—and with only modest efficacy and relatively poor tolerability of all currently available agents, a reality in AF management—results from ATHENA (A Trial with Dronedaron to Prevent Hospitalization or Death in Patients with Atrial Fibrillation) are that much more intriguing, as it is the first antiarrhythmic drug trial ever to demonstrate a distinct advantage for active therapy over placebo on important clinical outcomes.

As presented by Dr. Stuart Connolly, Professor of Medicine, McMaster University, Hamilton, Ontario, ATHENA was designed to evaluate the effect of dronedarone, a new multi-channel antiarrhythmic, on CV hospitalization or death as a primary outcome measure and to reassess its safety. Patients had either AF or atrial flutter lasting at least six months, the majority of whom were in sinus rhythm at the time of randomization. Patients received either dronedarone 400 mg b.i.d. (n=2301) or placebo (n=2327) and were followed for a minimum of 12 months, some for up to 30 months.

Approximately 30% patients in both treatment arms discontinued treatment during the course of the study, as Dr. Connolly reported, and the study was very well executed. Results showed that there was a 24% reduction in the primary end point of CV hospitalization or death from any cause in the

active treatment arm compared with placebo—“a highly significant finding,” as Dr. Connolly noted ($P<0.001$). There was also a 29% reduction in favour of dronedarone in CV death ($P=0.034$) and a 45% decrease in the risk of arrhythmic death—48 deaths in the placebo arm vs. 26 deaths in the active treatment arm. As Dr. Connolly also pointed out, it was particularly interesting to see that dronedarone reduced the incidence of acute coronary syndromes—“something that has never been shown before with an antiarrhythmic,” he added. Stroke was not a primary outcome in the trial but findings showed that there was a 34% decrease in the risk of stroke. Active therapy also appeared to reduce stroke for those on antithrombotic therapy as for those who were not, as Dr. Connolly observed.

Serious treatment-emergent adverse events were documented in 21% of placebo patients vs. 20% of those receiving active therapy, and dronedarone did not appear to be associated with any respiratory issues (unlike amiodarone). Non-CV death rates were very similar between the two arms, but CV death rates at 90 patients in the placebo arm compared with 63 deaths seen in the dronedarone arm were numerically higher.

Dr. Connolly addressed delegates, “We sometime ask, is there nothing we can do for our patients with AF, but this drug seems to have changed the way we can look at antiarrhythmic drugs now and perhaps there is something new we can do for these patients.”

Summary

During this important satellite symposium held on Saturday within the context of the CCC 2008 and chaired by incoming CCS president Dr. Charles Kerr, key opinion leaders shared a wealth of knowledge about the clinical implications of AF in the context of other diseases, including heart failure. Speakers also indicated how a patient-centred rather than an ECG-centred approach is the only meaningful strategy for patients with AF, and why a rate-control strategy is preferable to rhythm control in AF patients with heart failure. Delegates also heard about an exciting new multi-channel anti-arrhythmic drug that for the first time, has been shown to improve clinical outcomes in patients with AF, findings that augur well for a new era in AF management. □

Note: At the time of printing, dronedarone is not approved in Canada.

Based on:

“Reshaping the Future of Atrial Fibrillation Management.” Saturday, October 25, 2008, 14:30-16:30, Hall G.

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