

# Scientific Update™

XVIII™ CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY, AUGUST 25-29, 1996, BIRMINGHAM, UNITED KINGDOM

## Amiodarone: New Prophylactic Indications for an Old Drug?

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### Introduction: Is there real news in the treatment of arrhythmias?

The treatment of arrhythmias continues to be a therapeutic challenge. Despite decades of research in the primary and secondary prophylaxis of atrial and ventricular arrhythmias and sudden death, there is a perception that most, if not all, antiarrhythmic drugs are ineffective, highly toxic, or both. Despite this nihilistic sentiment, many clinicians consider that amiodarone may be an exception to the general rule for antiarrhythmic drugs. This ongoing uncertainty has led to a renewed interest in the evaluation of amiodarone. This issue of Scientific Update reflects this recent interest.

At the XVIIIth Congress of the European Society of Cardiology, five leading cardiologists participated in a symposium on the current state of amiodarone in the treatment of ventricular and supraventricular arrhythmias. The co-chairman, Dr. Philippe Coumel, pointed out that although amiodarone has been available for nearly 40 years and its antiarrhythmic properties were discovered over 25 years ago, it is a complex drug and new information on its efficacy and safety is becoming available even today. Five speakers then discussed new and important

data, including results of recent randomized clinical trials, examining the efficacy and safety of amiodarone in treating cardiac arrhythmias.

### Trials of amiodarone following acute MI

Dr. Desmond G. Julian, London, United Kingdom, discussed the results of the **European Myocardial Infarction Amiodarone Trial (EMIAT)**. This multicenter randomized controlled trial compared amiodarone to placebo in 1486 patients with recent myocardial infarction and left ventricular dysfunction, with an ejection fraction of < 40%. Patients received 800 mg of amiodarone for two weeks, 400 mg daily for 3½ months, followed by 200 mg a day. The primary end point was all cause mortality: the rate of death from all causes was virtually equal in the amiodarone and placebo groups, with a 13% cardiac mortality for both amiodarone and placebo. However, arrhythmic death (analyzed by intention to treat) was reduced by amiodarone from 50 to 33 deaths, and the sum of arrhythmic death and resuscitated VF from 61 to 42 events, both statistically significant ( $p < 0.05$ ). Considering the analysis of outcomes in patients actually receiving treatment, sudden deaths were reduced by nearly 50% from 45 in the placebo group to 23 in the amiodarone group. The

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The opinions expressed are only those of the Divisional members.  
This publication is made possible through unrestricted grants.

apparent explanation for the lack of reduction in overall and cardiac mortality compared to sudden cardiac death was due to an excess in deaths from reinfarction in the amiodarone group, 10 deaths vs 3 in the placebo group. Thirty-eight percent of patients on amiodarone discontinued therapy for adverse effects and other reasons, compared to 21% on placebo. There was a low rate of serious or life-threatening amiodarone toxicity, with a total of 3 respiratory deaths due to amiodarone induced pulmonary fibrosis and 1 death from pulmonary fibrosis in the placebo group. In interesting subgroup analyses, patients with more than 10 VPB's per hour on baseline Holter monitoring had a 20% mortality, compared to a 10% mortality in those with < 10 PVC's per hour, again confirming that baseline PVC's confer a risk of sudden and cardiac death. Beta-blockers in combination with amiodarone appeared highly beneficial, with a risk ratio of 0.5 for mortality with beta-blockers plus amiodarone vs beta-blockers plus placebo; in the absence of beta-blockers, mortality was similar in the amiodarone vs placebo groups. Although this is a retrospective assessment, it suggests that those patients administered beta-blockers derive not only overall benefit from the beta-blockers, but extra benefit from the amiodarone.

Dr. Julian concluded that amiodarone, as expected, yielded a 35% reduction in sudden cardiac death, but unexpectedly this did not translate into a reduction in cardiac or total death. He speculated that this may have been partly related to baseline imbalances in the amiodarone and placebo groups, an excess in competing causes of death not expected to be influenced by amiodarone, the play of chance, and a possible but unlikely adverse effect of amiodarone on non-arrhythmic death; of note, an excess in non-arrhythmic death has not been observed in any of the large studies of amiodarone to date, including CAMIAT, CHF STAT and others. He added that patients with higher heart rates, especially with baseline heart rates higher than 95 bpm, appeared to benefit the most from amiodarone. He concluded by stating that based on the EMIAT study, amiodarone can not be recommended routinely as prophylaxis for asymptomatic patients with low ejection fractions following myocardial infarction, but that if antiarrhythmic drug therapy is indicated for other reasons, it is safe and appears effective at reducing arrhythmic death.

Dr. John Cairns, currently Dean of Medicine at University of British Columbia and a member of

the Executive Committee of the **CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial)** discussed the outcome of this randomized controlled trial of amiodarone vs placebo. Patients in CAMIAT (n = 1202) all had more than 10 PVC's per hour on screening Holter monitoring between 6 and 45 days following myocardial infarction, and were randomized to placebo or 10 mg per kilogram of amiodarone per day for two weeks followed by maintenance doses of 400 mg a day, gradually reduced on the basis of VPB suppression on Holter monitoring. By the end of 4 months, the mean dose was 300 mg, and by the end of 12 months the mean dose was 200 mg a day. The prespecified primary outcome in this trial, unlike the EMIAT trial, was sudden cardiac death or resuscitated ventricular fibrillation (VF) based on an efficacy analysis (patients actually taking amiodarone for less than 3 months after discontinuation). There was 48.5% risk reduction in sudden death or resuscitated VF, being reduced from 6% on placebo to 3.3% at 2 years on amiodarone (p = 0.016, one sided). In the more conservative intention to treat analysis, there was still a 38% relative risk reduction from 6.9% to 4.5% on amiodarone. Total mortality was reduced, but not significantly, with an 18.3% relative risk reduction (p = 0.129), using an intention to treat analysis. Overall, mortality was 11.8% at 2 years in patients assigned to placebo, vs 9.9% in patients assigned to amiodarone. In this study, non-arrhythmic deaths were virtually identical in amiodarone and placebo groups. Amiodarone, as expected, was very effective at suppressing PVC's, with 84% of patients having near complete VPB suppression at 4 months. There was 14% excess of amiodarone early discontinuation over placebo (28% on placebo at 2 years vs 42% on amiodarone), almost entirely due to an excess in adverse events requiring discontinuation (13% on placebo, 26% on amiodarone). However, there were few life-threatening adverse events, and withdrawal for pulmonary toxicity was 3.8% on amiodarone vs 1.2% on placebo, with no deaths due to pulmonary toxicity; CNS toxicity 3.1% vs 0.8% and proarrhythmia was actually more frequent on placebo (3.0% vs 0.3% on amiodarone); although there was a substantial extent of asymptomatic biochemical hypothyroidism, symptomatic thyroid toxicity was rare.

Dr. Cairns concluded that amiodarone was effective at reducing arrhythmic death or resuscitated VF following acute myocardial infarction in patients with frequent PVC's at early Holter monitoring, and that there were favorable

trends in the other end points. Amiodarone effectively suppresses PVCs, and has a modest toxicity although discontinuation rates were relatively high. The relative risk reduction was the same in all subgroups assessed, including patients with remote myocardial infarction, prior heart failure, or increasing age; this results in a greater absolute risk reduction in such patients. In a question and answer period, he suggested that patients with frequent PVCs as well as poor left ventricular function may be the best target group for amiodarone therapy following myocardial infarction.

### Long term safety of amiodarone

Dr. Etienne Aliot from Nancy, France then discussed the long-term safety of amiodarone after myocardial infarction and in heart failure. He reviewed a number of randomized controlled trials with respect to the safety of amiodarone, including EMIAT, CAMIAT, the BASIS trial of amiodarone, the Polish trial of amiodarone following myocardial infarction, and the Spanish study on sudden cardiac death, all post infarction trials; he also discussed trials of amiodarone in heart failure patients, including the CHF STAT and the GESICA studies. He began by pointing out that unlike for class I antiarrhythmic drugs, none of these studies showed any trends to increasing mortality following amiodarone and some, such as the BASIS study, Polish study, and GESICA study showed a significantly decreased mortality. In a careful review of the toxicity from amiodarone in these trials, he noted that there was a moderate rate of drug withdrawal, but that serious toxicity was rare in all studies. In the BASIS study, 13% of patients had side effects requiring drug discontinuation, but there was no pulmonary toxicity or irreversible toxicity seen. In the Polish trial, 30% of patients had adverse effects and in 18% of them the drug was discontinued, compared to 10% and 6% on placebo respectively. There was only 1 case of amiodarone induced pulmonary toxicity. In the Spanish study, there was a 10% incidence of side effects requiring drug withdrawal. In the EMIAT study, pulmonary toxicity was seen in 17% of patients on amiodarone vs 7% on placebo, and there were 4 deaths possibly attributed to amiodarone pulmonary toxicity vs 1 from placebo, representing < 0.5% excess life-threatening toxicity. As noted above, the rate of pulmonary toxicity in CAMIAT was lower, 3.8% on amiodarone vs 1.2% on placebo.

In the GESICA study, there was a very low 6.1% incidence of symptomatic adverse effects on amiodarone, with a 4.6% withdrawal rate. In the CHF STAT study, there were 4 cases of pulmonary fibrosis on amiodarone vs 3 on placebo, and 6 cases of pulmonary adverse effects vs 1 on placebo and there were no reported deaths. He also noted that in the amiodarone treated patients there was a trend towards decreased death or hospitalization from heart failure in patients with nonischemic cardiomyopathy, and an increase by 8% in ejection fraction at 6 months vs a 3% increase in the placebo group. However, this increase in ejection fraction on amiodarone did not result in significant improvement in NYHA class.

He concluded by summarizing that amiodarone is virtually certainly safe even in ill patients following myocardial infarction or heart failure, and there was no trend in any study to increased mortality or increase in proarrhythmia from amiodarone. Side effects are relatively modest in this heterogeneous population. He noted that although asymptomatic (biochemical) thyroid disorders were common, symptomatic thyroid disorders occurred in only 2-4% of patients. Pulmonary toxicity appears to be much lower than previously believed, certainly < 3% and probably substantially lower. There was a 5% or less incidence of asymptomatic liver toxicity in these studies. Following a question from the audience, he stated that in his own practice, he does not consider biochemical hypothyroidism an indication for drug discontinuation, but merely for replacing thyroid hormone exogenously.

### Does the clinical setting influence amiodarone efficacy?

Dr. Gunther Breithardt, from Munster, Germany, summarized some of the perplexing contrasts between studies of amiodarone after myocardial infarction and in heart failure. He noticed that some studies showed more benefit in heart failure than in coronary disease whereas others the inverse. Some studies show more benefit in patients with well preserved LV function, whereas others show equal or greater benefit in patients with worse baseline LV function. He carefully reviewed all of the randomized controlled trials of amiodarone with respect to its effect on arrhythmic and overall mortality in various patient subgroups, and noted that there were perplexing discrepancies with respect to the subgroups that could not easily be resolved. He noted that amiodarone has multiple

electrophysiologic, vascular, and autonomic effects and that the studies had varying sample sizes, varying designs, varying doses, varying degrees of LV dysfunction and disease etiology in their patients enrolled, and varying adverse effect and discontinuation rates. Although the overall beneficial effects of amiodarone with respect to sudden death appear well founded, he cautioned against over interpreting the results of subgroup analyses in view of the small sample size and the discrepant extent of amiodarone benefit in varying subgroups in different studies.

### **Amiodarone in atrial fibrillation**

Dr. Stephen Hohnloser from Frankfurt, Germany, then discussed the use of amiodarone in atrial fibrillation. He noted that unlike for ventricular arrhythmias, there are no large randomized placebo controlled studies of amiodarone in the treatment of atrial fibrillation or mortality in atrial fibrillation. He noted that drugs in atrial fibrillation can be used to cardiovert to sinus rhythm, to maintain sinus rhythm once it is achieved, to control ventricular response during persistent or permanent atrial fibrillation, and must do so with an acceptable safety profile. In a meta analysis of available published trials containing a heterogeneous group of patients, he noted that amiodarone was effective in 64%, partially effective in 14%, and ineffective in 22%, with efficacy judged by the investigators. There is a very wide range of reported efficacy for cardioversion between 16 and 92%, varying by the route of amiodarone administration (IV vs po), the prior duration of atrial fibrillation, and the duration of drug administration. He noted that well controlled studies are required in this area. He reviewed some small studies which indicate that amiodarone can both restore sinus rhythm in longstanding atrial fibrillation, and facilitate the achievement of sinus rhythm by DC cardioversion and its subsequent maintenance. In the long run, sinus rhythm can be maintained following DC cardioversion in between 65 and 80% patients at one year. This rate appears to be greater than both for quinidine and flecainide, in meta analysis studies. He cautioned, however, that there are no prospective comparisons of amiodarone vs other therapies, and that these were needed before conclusions can be drawn about the relative efficacy of amiodarone compared to other antiarrhythmic drugs. He reported on very interesting results

from a placebo controlled randomized trial of amiodarone in heart failure (CHF STAT, referred to above), in which 103 patients were in atrial fibrillation at the beginning of the study, and after 4.5 years, 31% of patients assigned to amiodarone were in sinus rhythm compared to only 8% of those assigned to placebo. New atrial fibrillation developed in 23% on placebo vs 11% on amiodarone. These observations confirm the efficacy of amiodarone on atrial fibrillation even in patients with severe underlying cardiac disease.

### **Conclusion**

What is the practitioner to make of this large volume of data concerning the use of amiodarone? It is very clear from the accumulated studies that amiodarone is effective in preventing arrhythmic cardiac death and ventricular fibrillation, especially in patients with frequent PVC's after acute myocardial infarction. It is also clear that the drug is safe, perhaps safer than had previously been feared after early observational studies in patients with serious ventricular arrhythmias, where much higher doses were being used. The doses in the currently evaluated studies tended to be no greater than 300 mg, and often 200 mg per day as a long-term maintenance dose after initial loading. The risk of life-threatening pulmonary toxicity appears to be low at these doses, and side effects in all the studies were managed with dose reduction or drug discontinuation if necessary. There is near unanimous agreement that if antiarrhythmic therapy is required for symptomatic reasons, amiodarone is the most effective and safest drug in patients with left ventricular dysfunction or chronic myocardial scarring. There is intriguing evidence that amiodarone works especially well when combined with beta-blocker therapy. As prophylaxis to reduce overall mortality following myocardial infarction in all patients with frequent PVC's or poor LV function, amiodarone cannot be universally recommended, however, it is a drug of choice in certain patient subgroups. Although amiodarone is effective for patients with atrial fibrillation and severe underlying cardiac disease, more studies will be required before its true comparative value is clearly understood.