The Safety of Amiodarone in Patients With Heart Failure

CHRISTIAN TORP-PEDERSEN, MD,[1] MARCO METRA, MD,[2] PHILIP SPARK, PhD,[3] MARY ANN LUKAS, MD,[4] CHRISTINE MOULLET, MD,[5] ARMIN SCHERHAG, MD,[6] MICHEL KOMAJDA, MD,[7] JOHN G.F. CLELAND, MD,[8] WILLEM REMME, MD,[9] ANDREA DI LENARDA, MD,[10] KARL SWEDBERG, MD,[11] AND PHILIP A. POOLE-WILSON, MD,[12,*] FOR THE COMET INVESTIGATORS

Copenhagen, Denmark; Brescia, Italy; Nottingham, United Kingdom; Basel, Switzerland; Heidelberg, Germany; Paris, France; Kingston upon Hull, United Kingdom; Rhoon, Netherlands; Göteborg, Sweden; London, United Kingdom

ABSTRACT

Background: Uncertainty persists about the safety and efficacy of amiodarone for the management of heart failure.

Methods and Results: We randomized 3029 patients with chronic heart failure to receive carvedilol or metoprolol and followed patients for a median of 58 months. One hundred fifty-five of 1466 patients in New York Heart Association (NYHA) Class II and 209 of 1563 in Class III or IV received amiodarone at baseline. Persistence with amiodarone treatment was high and 66% received amiodarone after 4 years. During follow-up, 38.7% and 58.9% of patients receiving amiodarone in NYHA Classes II and III + IV died versus 26.2% and 43.3% not receiving amiodarone ($P < .001$). This difference was maintained in multivariable analysis (hazard ratio [HR] 1.5, 95% confidence interval [CI] 1.2−1.7, $P < .001$). The difference was explained by an increased risk of death due to circulatory failure (HR 2.4, CI 1.9−3.1, $P < .001$) in patients receiving amiodarone. Sudden death was not different (HR 1.07, CI 0.8−1.4, $P = .7$). The increased risk was similar across NYHA classes with HR of 1.60 (CI 1.2−2.1, $P < .001$) in NYHA Class II versus 1.58 (CI 1.3−1.9, $P < .001$) in Classes III + IV.

Conclusions: Treatment with amiodarone was associated with an increased risk of death from circulatory failure independent of functional class. (*J Cardiac Fail 2007;13:340−345*)

Key Words: Heart failure, circulatory failure, sudden death, mortality, amiodarone.

Amiodarone is an effective antiarrhythmic drug and along with dofetilide, it is the only recommended treatment to maintain sinus rhythm in patients with heart failure (HF) at increased risk of developing atrial fibrillation.[1] Amiodarone was evaluated for the prevention of sudden death in high-risk patients before β-blockers were widely used for HF. In the setting of chronic HF, 1 open-label trial[2] indicated a reduction in mortality with amiodarone but a double-blind trial versus placebo was neutral.[3] Recently, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated an overall neutral effect of amiodarone on mortality, compared with placebo, but a subgroup analysis showed increased mortality in patients with New York Heart Association (NYHA) Class III.[4] Thus the effect of amiodarone on mortality in patients with HF is uncertain. To provide further insights on this issue, we have analyzed the association between amiodarone therapy and mortality in the Carvedilol Or Metoprolol European Trial (COMET).[5] In this trial, 3029 patients with chronic HF treated with diuretics, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, and β-blockers were followed for a median of 58 months. This trial

From the [1]Department of Cardiology, Bispebjerg University Hospital, Copenhagen, Denmark; [2]Cattedra di Cardiologia, Università di Brescia, Italy; [3]Nottingham Clinical Research Group (NCRG), Nottingham, UK; [4]GlaxoSmikthKline, Philadelphia, Pennsylvania; [5]F. Hoffmann-La Roche, Basel, Switzerland; [6]I Medical Clinic, University Hospital Mannheim, University of Heidelberg, Germany and F. Hoffmann-La Roche, Basel, Switzerland; [7]La Pitié-Salpétrière Hospital, Paris, France; [8]Department of Cardiology, University of Hull, Kingston upon Hull, UK; [9]Sticares Cardiovascular Research Foundation, Rhoon, Netherlands; [10]Department of Cardiology, Ospedale di Cattinara, Trieste, Italy; [11]Department of Medicine, Sahlgrenska University Hospital/Östra, Göteborg, Sweden; and [12]National Heart and Lung Institute, Imperial College London, UK.

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Reprint requests: Prof. Christian Torp-Pedersen, Department of Cardiology, Bispebjerg University Hospital, 2400 Copenhagen NV, Denmark.

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[*] The COMET investigators are listed in a previous publication: Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomized controlled trial. Lancet 2003;362:7−13.

therefore represents a unique opportunity to assess the long-term effects on outcome related to concomitant amiodarone therapy. When this trial was started in 1996, amiodarone was likely to be used for a mixture of atrial and ventricular arrhythmias.

Methods

Details of the COMET study design have been published previously.[5–7]

A total of 3029 patients with chronic HF were recruited between 1996 and 1999. Patients were randomized to receive carvedilol or metoprolol tartrate. Follow-up was concluded in November 2002. An independent Data and Safety Monitoring Board monitored patient safety. All data were collected without knowledge of treatment allocation.

Patients

Major inclusion criteria were symptomatic chronic HF (NYHA Class II-IV), a requirement for diuretic therapy, at least 1 hospitalization for a cardiovascular reason within the last 2 years, on stable concomitant medication including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (if tolerated) for at least 4 weeks, and left ventricular ejection fraction below 35%. Relevant to this study, patients were excluded if they received >200 mg amiodarone per day, a class I antiarrhythmic drug, had symptomatic or sustained ventricular arrhythmia within the past 2 months not controlled with antiarrhythmic therapy or an implantable defibrillator, were treated with diltiazem or verapamil, were known to be intolerant to a β-blocker, or had diseases other than HF that could complicate therapy or shorten life expectancy.

Treatment and Measurements

At randomization, patients were assigned to treatment with carvedilol or metoprolol tartrate twice daily, titrated to a target dose of 25 mg carvedilol twice daily or to 50 mg metoprolol tartrate twice daily.

At the time of randomization, the use of all concomitant therapy, including amiodarone, was recorded.

Sudden Death and Circulatory Failure Death

Causes of death were evaluated by an end point committee blinded to treatment allocation. Sudden death was defined as witnessed or unwitnessed death in the absence of preexisting circulatory failure (see the following section) or other modes of death or patients resuscitated from a cardiac arrest in the absence of preexisting circulatory failure or other modes of death and who die within 24 hours or similar patients who die during an attempted resuscitation. Circulatory failure death required the presence at the time of death of cardiogenic shock (ie, hypotension for >15 minutes resulting in a failure to maintain normal renal or cerebral function before death), pulmonary edema sufficient to cause tachypnea and distress, HF symptoms or signs requiring continuous intravenous therapy or oxygen administration, or confinement because of HF symptoms.

Statistical Analyses

The table of baseline characteristics presents 4 groups based on amiodarone use and NYHA classification at baseline. However, the *P* values relate to the differences between the subjects receiving and not receiving amiodarone. The differences were assessed by *t*-tests for continuous variables and chi-squared tests for categorical data.

Univariate analysis of survival according to the use of amiodarone was performed with the log-rank test and mortality curves were generated by the Kaplan-Meier method. Multivariable comparisons were performed with Cox proportional hazard models. Hazard ratios (HR) are given with their respective 95% confidence intervals (CI).

To assess the impact of baseline characteristics on our conclusions, we developed a multivariate Cox proportional hazards model for all-cause mortality using bootstrap methods. As a form of internal validation, 200 samples of 3029 patients (sampling with replacement) were taken and a backwards stepwise procedure run on each sample. For each sample, the variables selected were recorded. Variables appearing in 70% or more of all models are included in our final multivariate model. The included variables were study medication; age; gender; systolic blood pressure; NYHA class; duration of HF; left ventricular ejection fraction; electrocardiographic results; diuretic dose; use of digitalis; use of lipid lowering agents; and levels of hemoglobin, sodium, and creatinine.

As a validation of the results, propensity score matching was used to construct a set of cases and controls on which to run the univariate and multivariate models. Stepwise procedures were used to construct a logistic regression model for the incidence of amiodarone at baseline. From this logistic model, predicted probabilities (propensity scores) were obtained for each patient. The cases (amiodarone used at baseline) were matched to controls (no amiodarone used at baseline) by these scores in 358 cases. Five cases were not matched because of missing propensity scores, and 1 case because of no available matches at 1 decimal place. The univariate and multivariate models were then ran on these restricted 716 patients.

Results

The 3029 patients randomized to carvedilol (1511 patients) or metoprolol tartrate (1518 patients) were followed for a median of 58 months (interquartile range 54 to 64 months). Follow-up was complete except for 33 patients who were lost to follow-up (n = 5) or who withdrew consent (n = 28) during the trial. Of 1466 patients in NYHA II and 1563 in NYHA III, 155 (10.6%) and 209 (13.4%), respectively, were receiving amiodarone at baseline (Table 1). The majority of differences were statistically significant