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Dofetilide in Patients with Left Ventricular Dysfunction and either Heart Failure or Acute Myocardial Infarction: Rationale, Design, and Patient Characteristics of the DIAMOND Studies

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Summary

Background: Attempts to prolong life with antiarrhythmic drugs in patients at increased risk of sudden cardiac death have so far been disappointing or inconclusive.

Hypothesis: The Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) encompass two survival studies testing the prophylactic use of the selective potassium-channel blocker, dofetilide, in patients at high risk of sudden death.

Methods: The first study includes patients admitted to hospital with congestive heart failure (CHF), the other includes patients with acute myocardial infarction (MI) within the previous 7 days. In both studies patients must have left ventricular systolic dysfunction (ejection fraction ≤35%) determined by echocardiography. Each of the two studies are planned to enroll 1500 patients. Consecutive hospitalized patients with MI or CHF are screened in 37 Danish hospitals. Eligible patients are randomized to receive dofetilide or matching placebo. All patients are continuously monitored by telemetry for the first 3 days of the study to detect possible arrhythmic events and to ensure resuscitation in case of serious arrhythmias. Minimum duration of follow-up is 12 months.

Results: Between November 1993 and July 1996, a total of 5812 consecutive patients with CHF and 8688 consecutive patients with MI was screened for entry. Of these, 1518 patients were included in the CHF study and 1510 patients in the MI study. Overall 1-year mortality of randomized patients were 28 and 22%, respectively.

Conclusion: DIAMOND will provide important data on the safety and efficacy of dofetilide in high-risk patients with left ventricular dysfunction and either CHF or MI, as well as evaluate tolerability in these populations.

Key words: congestive heart failure, myocardial infarction, left ventricular dysfunction, prognosis, dofetilide

Introduction

Attempts to prolong life with antiarrhythmic drugs in patients at increased risk of sudden cardiac death have so far been disappointing or inconclusive. In the Cardiac Arrhythmia Suppression Trial (CAST),[1] the sodium-channel blockers (class 1C) encainide and flecainide increased mortality compared with placebo. Increased mortality compared with placebo was also demonstrated with the potassium-channel blocker d-sotalol in the Survival With Oral D-Sotalol trial (SWORD).[2] Amiodarone reduced mortality in one open study,[3] but this result was not confirmed in several other studies.[4–7]

The area of prevention of sudden death by drug treatment currently is a therapeutic void and, with the increased mortality on active therapy described in several studies, safety will be a key issue in future studies. Antiarrhythmic drugs can cause serious arrhythmias, and the mortality observed in studies may represent a net result of a beneficial effect of the drug that is countered by the harmful effect of proarrhythmia. Since low overall mortalities were observed in clinical studies, the likelihood of detecting a beneficial effect can be increased when a high-risk population is selected.

Dofetilide is a new highly selective inhibitor of the rapid component of the delayed rectifier potassium current (I_{Kr}).[8] Consequently, it prolongs action potential duration and the effective refractory period in a concentration-dependent manner.[8,9] The drug is hemodynamically neutral and has no effect on atrioventricular (AV) node conduction or sinus node function in humans.[10,11] Clinical studies have demonstrated that dofetilide is effective in the conversion of atrial fibrillation and supraventricular tachycardias and in maintaining sinus rhythm in patients with atrial and ventricular arrhythmias.[12–14] It is well tolerated and is associated with a low and dose-dependent incidence of proarrhythmia (data on file, Pfizer Central Research).

Based on the ability of dofetilide to maintain sinus rhythm in patients with ventricular arrhythmias and its neutral effect on hemodynamics, we hypothesized that long-term treatment

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with dofetilide may prolong life in patients at high risk of death due to ventricular arrhythmias. Patients with congestive heart failure (CHF)[15, 16] and patients with reduced left ventricular (LV) function[17, 18] following a myocardial infarction (MI) represent large groups of patients at high risk of arrhythmic death. Thus, the Danish Investigations of Arrhythmia and Mortality ON Dofetilide (DIAMOND) were designed as two separate, randomized studies of dofetilide in patients with CHF or MI associated with LV dysfunction. This publication describes the design of the studies, including specific features to ensure representative patients, and presents characteristics of patients screened and randomized.

Patients and Methods

The main purpose of the two studies is to demonstrate whether dofetilide can safely reduce mortality and morbidity in patients with moderate to severe systolic LV dysfunction and either CHF or a recent MI.

Design

The DIAMOND studies are two separate randomized, double-blind, placebo-controlled, parallel group studies conducted on a multicenter basis at 37 hospitals in Denmark.

Consecutive patients with either CHF or recent MI are screened and as many as possible entered to ensure a representative study population. Screening is performed after provision of written informed consent and consists of medical history and an echocardiographic examination recorded on videotape (see below). The consecutive screening is an important feature that ensures that high-risk patients are given the opportunity of being randomized rather than being selectively excluded by physician bias.

Patients of non-childbearing potential, aged ≥18 years, are considered for inclusion in the studies if they exhibit LV systolic dysfunction, defined as a wall motion index ≤ 1.2 (which corresponds to an LV ejection fraction of ≤ 35%[19]), if they are hospitalized with either CHF or MI. Myocardial infarction is defined as chest pain lasting for > 20 min and/or electrocardiographic (ECG) changes indicative of MI accompanied by significant elevation of cardiac enzymes. Patients with CHF are identified based on history or are newly diagnosed as requiring treatment. Congestive heart failure is defined as a recent (within 1 month) history of shortness of breath, either at rest or upon minimal exertion, or paroxysmal nocturnal dyspnea. Patients must be enrolled 3 to 7 days after the MI or hospitalization with CHF/development of CHF. The criteria have been selected to ensure that patients randomized are at high risk of arrhythmic cardiac death. Patients not meeting exclusion criteria (Table I) are enrolled upon provision of written informed consent.

TABLE I Exclusion criteria

Resting ventricular rate of < 50 beats/min when awake and at time of randomization
Sick sinus syndrome unless treated with a well-functioning pacemaker
Second- or third-degree AV block at time of randomization unless treated with a well-functioning pacemaker
History of polymorphic VT secondary to treatment with antiarrhythmic drugs or with other drugs which have been shown to be associated with the genesis of TdP VT
QTc interval exceeding 460 $ms^{1/2}$ in the drug-free state at the time of randomization. In case of increased QRS width, e.g., due to BBB, a QTc interval of up to 500 $ms^{1/2}$ will be accepted
Diastolic blood pressure > 115 mmHg or systolic blood pressure < 80 mmHg at time of randomization
Patients who are likely to die from other causes during the course of the study (e.g., cancer, including treatment with antineoplastic drugs)
Serum potassium < 3.6 mmol/l or > 5.5 mmol/l at time of randomization
Concomitant therapy with class I or III antiarrhythmic drugs, or those receiving such treatment in the period of time corresponding to five times the relevant half-life prior to receiving study treatment
Amiodarone treatment within the last 3 months
Patients taking part in experimental drug studies in the previous 3 months
Patients who have previously received dofetilide
Chronic alcoholism, drug addiction, dementia, or other conditions under which the patient cannot cooperate in the study
Creatinine clearance < 20 ml/min or clinically significant liver dysfunctions, e.g., cirrhosis
Patients on urgent cardiac transplantation list
Acute myocarditis
Planned cardiac surgery including surgery for valvular heart disease, CABG and PTCA
Aortic stenosis
Cardiac surgery within the preceding 4 weeks
Implanted cardioverter defibrillator

Abbreviations: AV = atrioventricular, VT ventricular tachycardia, TdP = torsade de pointes, BBB = bundle-branch block, CABG = coronary artery bypass grafting, PTCA = percutaneous transluminal coronary angioplasty.

Study Organization

The Danish Board of Health and the Central Danish Ethics Committee have given permission to carry out the DIAMOND studies, which are conducted in accordance with the Declaration of Helsinki II and guidelines for Good Clinical Practice in the European Union. The study is led by a Steering Committee that functions independently of the sponsor. An independent Data and Safety Monitoring Board receives regular, unblinded updates of serious adverse events, potential proarrhythmic events and deaths, along with four preplanned interim analyses of mortality. Based on these data, the Data and Safety Monitoring Board can recommend continuation, extension, or premature termination of each of the studies to the Steering Committee. An Events Committee classifies all deaths that occur in the two studies as being of cardiac or noncardiac origin, blinded to the type of treatment the patient has received. Cardiac deaths are adjudged as being arrhythmic or not, with arrhythmic deaths being subdivided into presumed or documented according to the available evidence. An Arrhythmia Subcommittee classifies arrhythmic events that take place during the study, including ventricular tachycardia (VT), ventricular fibrillation (VF), and torsade de pointes (TdP) VT. An Executive Committee serves to interface between the Steering Committee and the participating centers. Management and monitoring of the studies within Denmark is conducted by a contract research organization, Medicon A/S. Committees and participants are listed in Appendix I.

Statistical Analyses

The sample size is based upon the hypothesis that there will be a 25% reduction of relative mortality risk in the patients treated with dofetilide. One-year mortality figures of approximately 25%[15] and 30%[20] are expected in the placebo groups of the CHF and MI studies, respectively. Thus, given a mean duration of follow-up of 2 years, 1,050 patients are needed in the CHF study and 848 patients are needed in the MI study so that statistical differences between the placebo and dofetilide groups may be detected at the 5% significance level with a 90% power. Sample size calculations are based on a method for estimating survival times from two independent groups with limited recruitment and censoring.[21] To take into account the potential for a lower level of placebo mortality than initially expected and for a proportion of deaths being of nonarrhythmic etiology, a total of 1,500 patients will be randomized into each of the studies.

Analysis of time-to-events will be compared using the log rank test. Supplementary analyses will employ Cox proportional hazard analysis.

Outcome Variables

End points are identical for the two studies and are listed in Table II. The Events Committee classifies death as cardiac if there is no specific evidence that death is noncardiac. Similar to CAST,[22] cardiac death is classified as presumed arrhythmic if there is no specific evidence to suggest nonarrhythmic death. In contrast to CAST, resuscitated cardiac arrest is not counted as death. Documented arrhythmic death requires that the fatal arrhythmia has been documented with an ECG. Incidence of arrhythmia requiring treatment and withdrawal from study drug is registered by the investigator, who is requested to specify this end point at each visit.

For each of the two studies, prespecified subgroups to be analyzed are separated into two populations on the basis of median age, gender, previous MI, smokers, diabetes, hypertension, CHF (MI study), median renal clearance, median wall motion index, median heart rate variability, and, upon the presence or absence of previous MI, diabetes, hypertension, CHF (MI study), ischemic/nonischemic cause of CHF (CHF study), thrombolytic therapy, (MI study), beta-blocker therapy, and atrial fibrillation at the time of randomization. Subgroups by New York Heart Association (NYHA) class will also be analyzed.

TABLE II Outcome variables

Primary
All-cause mortality (i.e., time to death)
Secondary
Cardiac mortality
Incidence of TAD
Incidence of arrhythmia requiring treatment and withdrawal of study drug
Cardiac mortality plus resuscitated cardiac arrest
Number of infarctions/reinfarctions and worsening of CHF
In patients with atrial fibrillation at baseline, separate analysis of total mortality/number of strokes/number of systemic embolisms will be performed
Total mortality, cardiac mortality, and incidence of TAD in patients randomized from the time of the implementation of the protocol amendment allowing for dosage reduction according to the creatinine clearance. The cut-off date was May, 1, 1994
Total mortality, cardiac mortality, and incidence of total arrhythmic death for the first year of treatment after randomization
Total mortality, cardiac mortality, and total arrhythmic death in the CHF and MI studies combined

Abbreviations: TAD = total arrhythmic death, CHF = congestive heart failure, MI = myocardial infarction.

Randomization

Eligible patients are assigned to treatment by means of a computer-generated pseudo-random code, and separate randomizations are performed for the CHF and MI studies; patients who exhibit both CHF and a recent MI (within 7 days) are allocated to the MI study. Patients in both studies are stratified according to center and degree of LV dysfunction (wall motion index < 0.8 and wall motion index ≥ 0.8).

Dosing Regimen

Three dosage levels are used: 500 mcg b.i.d., 250 mcg b.i.d., and 250 mcg o.d. Patients in sinus rhythm receive dofetilide 500 mcg b.i.d. or corresponding placebo. If creatinine clearance is reduced or the patient has atrial fibrillation/flutter (Afl) at randomization, the dose is reduced to 250 mcg b.i.d. (or placebo) or 250 mcg o.d. (or placebo). With the higher doses, stepwise dose reduction is made if creatinine clearance decreases or if there is an increase in QTc interval exceeding 20% from baseline or exceeding 550 ms.[23] If QTc does not fall below an acceptable limit within 2 days, further dose reduction is performed. If a dose reduction is required at the lowest possible dose study, medication is discontinued. Dose reduction can also be performed because of an adverse event or at the discretion of the investigator.

At the outset, dose limitation linked to reduction in creatinine clearance was not a requirement. After recruitment of approximately 550 patients in the two DIAMOND studies, a multivariate anal-ysis of the drug sponsor's (Pfizer Central Research) global dofetilide safety database (without cases from DIAMOND) identified creatinine clearance as a guiding principle for dosing patients to avoid overexposure to the drug in patients with impaired renal function. This was supported by a study of plasma dofetilide concentrations in patients with reduced renal function (unpublished data on file, Pfizer Central Research) and led the Steering Committee to implement a dose reduction in patients with impaired renal function.

Electrocardiographic Monitoring

A baseline 12-lead ECG is obtained prior to administration of study medication, and further ECGs are recorded 2–4 h after the first dose as well as 2–4 h after the morning dose on Days 2 and 4 of treatment. The patients are monitored by continuous telemetry in hospital for the first 72 h of study treatment to ensure recognition of arrhythmic events and to enable immediate resuscitation in case of cardiac arrest.

When feasible, Holter monitoring is performed on the day prior to inclusion and on Day 3 of treatment.

Follow-Up

The patients are seen on an outpatient basis 1 month after inclusion. Clinical evaluation, laboratory safety tests, and adverse events are recorded, and a 12-lead ECG including measurement of QTc is obtained. Similar examination is subsequently undertaken for each patient every 3 months after initiation of therapy, until the end of each study. Each study will be completed 12 months after the recruitment of the last patient. After 1 year of treatment, laboratory safety tests are obtained on a 6-monthly basis.

Interim Analyses

Interim analyses of the primary end point all-cause mortality are planned in each study after 50, 100, 200, and 300 deaths. The outcomes are sent only to the Data and Safety Monitoring Board. Asymmetric stopping guidelines are used and weaker evidence is required to stop one of the studies if there is an indication of harm, while premature stopping due to efficacy will only be considered if dofetilide is clearly superior to placebo.

Echocardiography

The echocardiographic method used has been validated and described in detail elsewhere.[20] The method has not been validated for patients with CHF without MI, and this is being performed during the study. Staff at participating centers have received training in echocardiographic examination, focusing on imaging technique. Left ventricular dysfunction, defined by a wall motion index ≤ 1.2 (corresponding to an ejection fraction of approximately 35%[19]), is determined by central evaluation of videotaped echocardiographic examinations undertaken at each of the centers, using standard echocardiographic views. For evaluation of wall motion index, a 16-segment model is employed,[24] using a scoring system where -1 represents paradoxical movement, 0 is akinesia, 1 is hypokinesia, 2 is normokinesia, and 3 is hyperkinesia.[25]

Results of Patient Selection

Between November 1993 and July 1996, 5,810 patients were screened for the CHF study, and 8,688 for the MI study. Demographic data and 1-year mortality for patients screened are shown in Table III and for those randomized into the study in Table IV. Recruitment ended in November 1995 for the CHF study and in July 1996 for the MI study.

As of March 1, 1997, 25 cases of torsade de pointes have been identified in the CHF study, and 6 cases in the MI study. Of these, 24 have occurred within the first 3 days after randomization (19 in the CHF study, and 5 in the MI study) while the patients were on continuous telemetry.

During the study, 16 patients in the CHF and 22 in the MI study discontinued treatment due to prolongation of QTc interval and 190 and 168, respectively, withdrew consent. In addition, 50 and 30 patients, respectively, reached the end point of cardiac arrest with resuscitation.

Conclusion

The DIAMOND studies are designed to evaluate the safety and efficacy of a new selective potassium-channel blocker, dofetilide, in high-risk patients with recent myocardial infarc-

TABLE III Baseline demographics and 1-year mortality of the first 5,812/8,688 patients screened for entry into DIAMOND

	CHF study	MI study
No. of patients	5,812	8,688
Mean age (years)	72 (10)[a]	67 (12)[a]
Male (%)	60	70
Hypertension (%)	24	24
Diabetes (%)	17	11
Previous MI (%)	38	26
Acute anterior MI (%)	N/A	40
Wall motion index ≤ 1.2	45	28
NYHA class I	2	11
NYHA class II	21	21
NYHA class III	41	19
NYHA class IV	19	17
NYHA class not available	17	32
1-year Kaplan-Meyer mortality	24	16

[a] Figures in parentheses = standard deviation.
Abbreviations: CHF = congestive heart failure; MI = myocardial infarction; N/A = not applicable, NYHA = New York Heart Association.

TABLE IV Baseline demographics and 1-year mortality of the first 1,518/1,510 CHF/MI randomized patients

	CHF study	MI study
No. of patients included	1,518	1,510
Mean age (years)	70 (10)[a]	69 (11)[a]
Male (%)	73	74
Hypertension (%)	24	23
Diabetes (%)	20	13
Previous MI (%)	51	36
Acute anterior MI (%)	N/A	63
Median wall motion index	0.9 (0.2)[a]	1.0 (0.2)[a]
NYHA class I	<1	4
NYHA class II	15	19
NYHA class III	51	25
NYHA class IV	21	23
NYHA class not available	12	29
1-year Kaplan-Meyer mortality	28	22

[a] Figures in parentheses = standard deviation.
Abbreviations as in Table III.

tion or congestive heart failure combined with systolic left ventricular dysfunction. Continuous telemetry for the first 3 days after randomization has proved valuable in detecting and enabling treatment of tachyarrhythmic events. The studies are expected to conclude follow-up by mid 1997, with the results available shortly thereafter.

Appendix

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