Original articles

The ALPHA study (T-wave ALternans in Patients with Heart fAilure): rationale, design and endpoints

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Key words:
Arrhythmias, ventricular; Dilated cardiomyopathy; Heart failure; Sudden cardiac death; T-wave alternans.

Background. **Sudden death and pump failure are the main causes of death in patients with heart failure. Patients with ischemic and non-ischemic cardiomyopathy are at similar risk of arrhythmic mortality; however, standard non-invasive and invasive tests are not routinely available for non-ischemic patients. T-wave alternans (TWA) has been proposed as a potential marker of susceptibility to ventricular tachycardia-fibrillation in several groups of patients.**

Methods. **The ALPHA study was designed to evaluate the independent predictive value of the measurement of microvolt TWA on the combined occurrence, after 18 months of follow-up, of cardiac death and life-threatening arrhythmias in a population of patients with non-ischemic dilated cardiomyopathy and NYHA class II and III. This is a multicenter prospective observational study. A total of 370 patients, with measurable TWA, will be enrolled during routine follow-up for heart failure treatment; a logbook will be used to collect basic information on the whole screened population. Patients will be enrolled during a 2-year period and will be followed up for 18 months. The primary endpoint of the study will be the combined incidence of cardiac death and life-threatening ventricular arrhythmias. The study will complete recruitment by mid 2004 and report in 2006.**

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Introduction

Heart failure (HF) is a syndrome that affects over 6.5 million Europeans with 580 000 new cases diagnosed annually[1]. Left ventricular dysfunction, reduced exercise tolerance, and ventricular arrhythmias are all associated with this condition[2]. The prognosis is typically poor, with a 1-year all-cause mortality of approximately 12-15%[3-5]. Sudden death and pump failure due to progressive HF are the main causes of death in these patients. The goals of therapy are to minimize symptoms, improve functional capacity, and increase survival[6]. However, despite the continuous progress in the medical treatment of patients with HF, the mortality remains extremely high. Notably, a significant proportion of the mortality among patients in NYHA class II and III is due to ventricular tachyarrhythmias. Among antiarrhythmic drugs, amiodarone is the only agent that has been shown not to increase mortality[5]. However, large randomized placebo-controlled clinical trials of amiodarone in patients with severe HF have yielded mixed results[5,7]. Device therapy has been shown to reduce the total mortality in patients with ventricular tachyarrhythmias in randomized clinical trials comparing antiarrhythmic drugs and implantable cardioverter-defibrillators (ICD)[8,9]. Among patients with ischemic heart disease, both non-invasive and invasive predictors of arrhythmic events have been identified; specifically, in post-infarction patients with left ventricular dysfunction clinical evidence shows a survival benefit with the use of an ICD[8,9]. Although patients with non-ischemic dilated cardiomyopathy are similarly at high risk of arrhythmic mortality, the current screening methods have been shown to have a very low positive predictive value and are of limited value in the identification of those patients who could benefit from an ICD. Microvolt T-wave alternans (TWA) has been proposed as a potential marker of susceptibility to

sustained ventricular tachycardia and fibrillation (VT/VF) in several populations of patients[10-13]. Preliminary data have suggested that TWA may be useful for the screening of patients who are at high risk of VT/VF among those with congestive HF, both of ischemic and non-ischemic origin, left ventricular ejection fraction ≤ 40%, NYHA class II or III and no history of VT/VF[14].

Methods

Study purpose. The goal of this study is to evaluate the independent predictive value of the measurement of microvolt TWA on the combined occurrence, after 18 months of follow-up, of cardiac death and life-threatening arrhythmias in a population of patients with non-ischemic dilated cardiomyopathy and NYHA class II and III.

Study design. This is a multicenter prospective observational study. Nine Italian centers with experience in the treatment of both HF patients and in the implantation of ICD are participating. The investigation conforms to the principles outlined in the Declaration of Helsinki.

The study includes patients seen during routine follow-up for HF treatment; a logbook is being used to collect basic information on the whole population screened. The study has been designed in such a way as not to vary or alter the standard care for this patient population at any single center; therefore, patients in NYHA class III and with left bundle branch block causing a QRS duration ≥ 150 ms are candidates for cardiac resynchronization therapy (CRT) using a biventricular device (pacemaker alone or with defibrillation backup). Similarly, patients with no current ICD indication may receive an ICD on the basis of the investigator's clinical judgment.

Patient eligibility. The study inclusion and exclusion criteria are shown in table I. Patients with non-ischemic dilated cardiomyopathy in NYHA class II and III are eligible for the study. Patients must be in stable clinical conditions (see below) and treated with the best medical treatment, including (if tolerated) ACE-inhibitors, diuretics and beta-blockers. Digitalis may be given following the decision of the investigator. During the study, care is being taken not to change the treatment regimen in the absence of appropriate clinical grounds. Any contraindication or intolerance to the above-mentioned drugs must be fully described.

Table I. Inclusion and exclusion criteria.

Inclusion criteria
1. Patients with heart failure (NYHA class II or III) and *with* left ventricular ejection fraction ≤ 40%, and stable clinical conditions.
2. Non-ischemic cardiomyopathy.
3. Patient age ≥ 18 years and ≤ 80 years.
4. Patients should be on optimal individual drug therapy without any change within the last 14 days and including:
   - ACE-inhibitors (unless not tolerated)
   - beta-blockers (unless not tolerated)
   - diuretics (unless not tolerated)

Exclusion criteria
1. Life expectancy ≤ 6 months.
2. Patients who despite adequate medical treatment (including diuretics, ACE-inhibitors and beta-blockers if tolerated) have been in NYHA class IV during the previous 6 months.
3. Permanent atrial fibrillation or treatment-refractory atrial flutter.
4. A history of syncope of known arrhythmic cause, or the documentation of an episode of ventricular tachycardia at a rate > 150 b/min and lasting > 10 s during the previous year.
5. Class I indications for conventional pacemaker therapy (chronotropic incompetent patients may be included).
6. Patients who already have an implanted ventricular pacemaker.
7. Conventional implantable cardioverter-defibrillator indications.
8. Any cardiac surgery within the previous 3 months.
9. Patients who are candidates for cardiac surgery (with the exception of heart transplantation).
10. Arrhythmogenic right ventricular dysplasia
11. Renal insufficiency requiring hemodialysis.
12. Severe chronic obstructive pulmonary disease requiring O_2 therapy.
13. Patients with restrictive or hypertrophic obstructive cardiomyopathy.
14. Endocrine disorders such as uncontrolled diabetes mellitus, pheochromocytoma, active hyperthyroidism and untreated hypothyroidism.
15. Known drug or alcohol abuse.
16. Patients unable to adequately perform the exercise test.
17. Patients who live too far from the referring center or other reasons that render follow-up impossible.
18. Patients who do not give informed consent.
19. Referring physician or general practitioner do not agree with the patient's enrollment.
20. Mentally disabled patients.
21. Pregnant women.

Endpoints

Primary endpoint. The primary endpoint of the study will be the combined incidence of cardiac death and life-threatening ventricular arrhythmias over the 18-month follow-up period in the whole population of patients. Life-threatening ventricular arrhythmias will include VF, resuscitated cardiac arrest, sustained symptomatic VT and appropriate intervention, or VT detection by the implanted electrical device (ICD or biventricular pacemaker).

In this subgroup of implanted patients, automatic electrogram storage will be appropriately programmed to detect malignant ventricular arrhythmias defined as all of the above-mentioned events as well as VTs with a rate > 150 b/min and a duration > 10 s.

Secondary endpoints. The secondary endpoints of the study will include the evaluation of the prognostic value of the TWA for:
• total mortality and the combined incidence of sudden death and life-threatening ventricular arrhythmias;

• hospitalization rate, length and causes;
• an extended combined endpoint, in the subgroup of patients with a device implanted within 1 month of enrollment (implanted population), including the presence of sustained symptomatic VT and appropriate intervention or VT detection by the implanted electrical device (ICD or biventricular pacemaker);
• cardiac death and malignant ventricular arrhythmias in the subgroup of patients implanted with a biventricular pacing device.

An additional endpoint will be the evaluation of changes at 12 months of TWA measurements and of the functional improvement in the population submitted to CRT as assessed by cardiopulmonary exercise examination, echocardiography and the Minnesota Living with HF© survey tool.

Sample size

Definition. The calculation of the sample size relies on the primary endpoint (Table II) and is based on the following assumptions, partly taken from Klingenheben et al.[14].

The choice of conservative values for alpha (1%) and power (90%) results in a large sample size thus reducing, to some extent, the impact of over fitting when including confounders in the analysis of the prognostic role of TWA. The software nQuery 4.0 (StatSol, Cork, Ireland) has been used for computation.

Some patient attrition is expected from this population. Attrition could occur due to loss to follow-up, or to lack of adherence to the study design. Assuming a 10% attrition rate during the study, the total sample size to analyze the prognostic value of positive TWA will amount to 316 patients with measurable TWA.

On the basis of an expected undetermined TWA rate of 25%, 72 additional patients will undergo TWA measurement.

Refinement. In September 2003, with 307 patients enrolled, the distribution of TWA appeared to markedly differ from what assumed in the planning phase of the study, and was in accordance with the data recently published by Hohnloser et al.[15]. Moreover, the increased use, in the past few years, of carvedilol and of CRT in such patients, would certainly reduce the incidence of events during follow-up[16]. On the basis of these new elements, we felt the need to reassess the size of the study, with less rigid, although acceptable values both for alpha (5%) and power (80%), to allow for feasibility. The hypothesized proportion of events was lower than in Hohnloser's paper, due to the different inclusion criteria and event definition in our study population (Table III).

Attrition could be due to loss during follow-up or to lack of adherence to the study design. Assuming a 10% attrition rate during the study, the total sample size to analyze the prognostic value of positive TWA will amount to 370 patients with measurable TWA.

On the basis of an expected undetermined TWA rate of 21%, 89 additional patients will undergo TWA measurement.

These changes required a protocol amendment.

Table II. Sample size definition.

TWA prevalence	17%
Rate of events at 12 months in TWA- patients	1%
Rate of events at 12 months in TWA+ patients	15%
Alpha error	1%
Power	90%
No. patients	287
No. TWA-	239
No. TWA+	48

TWA = T-wave alternans.

Table III. Sample size refinement.

Type I error/power	5%/80%
Distribution of TWA+ and TWA-	58% and 42%
Probability of events at 18 months for TWA+ and TWA-	11% and 3%
No. TWA+ and TWA- cases	195 and 141
No. patients with determinable TWA	336

TWA = T-wave alternans.

Study flow

Each center followed its hospital policy regarding review of the clinical investigation by the Ethics Committee. Each patient is required to give informed written consent prior to enrollment in the clinical investigation, after the investigator has explained the reason for the study, the risks and benefits.

Patients are screened at each center and enrolled and followed up with assessments every 6 months up to 18 months. Patient enrollment and follow-up evaluation included the procedures listed in table IV.

Diagnostic test and screening at baseline

T-wave alternans. *Recording equipment.* The TWA test involves the simultaneous recording of a 12-lead ECG and orthogonal ECG using the Cambridge Heart CH-2000 stress test system or a similar successor system equipped with 14 electrodes: 7 standard electrodes and 7 Cambridge Heart alternans sensors. The CH-2000 is a computer-based ECG exercise tolerance test system intended for the recording of ECGs and vectorcardiograms. The TWA test is performed at baseline in all patients. It is repeated at pre-discharge and at 6 and 12 months in the implanted population only.

Table IV. Diagnostic procedures.

	Baseline	Pre-discharge	6 months	12 months	18 months
T-wave alternans	*	**	**	**	
Echocardiography	*		**	**	
Holter	*		**		
Cardiopulmonary exercise test	*		**	**	
Quality of life	*		*	*	*
No. hospitalizations in the previous 6 months			*	*	*
Events during the previous 6 months			*	*	*

* procedures to be performed in every patient; ** procedures to be performed only in patients implanted with biventricular devices.

Protocol. Once the skin preparation is completed and all sensors applied and connected to the Cambridge Heart 2000 computer, the ECG is recorded with the patient motionless. Immediately following the rest recording, submaximal exercise testing is performed on a treadmill, according to the Naughton or the modified Bruce protocol, or on a bicycle ergometer. If the exercise test is performed on a bicycle ergometer, the exercise is tailored to the individual patient, usually starting at 10 W, with a stepwise increment of 10 W/min. Care should be taken not to elevate the heart rate too quickly. The ECG is recorded during exercise to a target heart rate of 120 b/min, unless terminated earlier because of fatigue or other symptoms. All efforts should be made to elevate the heart rate gradually as close as possible to 120 b/min for at least 1 min, since this level of exercise is the most likely to achieve determinable TWA results. Following the exercise recordings, at least 5 min of recovery ECG data are registered. The heart rate and blood pressure are measured at rest, during each stage of exercise and at peak exercise using a sphygmomanometer. The TWA examination is performed at baseline (enrollment) and its result will be evaluated in accordance with "B" rules[17] by the site investigator in order to define a patient as positive, negative or indeterminate.

Echocardiography. Standard echocardiographic parameters are recorded at baseline in all patients. Echocardiography is repeated during follow-up at 6, 12 and 18 months only in patients implanted with a biventricular device. The left ventricular ejection fraction is measured using the conventional area-length method.

Holter monitoring. A 24-hour Holter monitoring is recorded in all patients at baseline, during normal daily activity. It is repeated during follow-up at 6 month only in patients implanted with a biventricular device. Each beat is targeted as normal or aberrant on the basis of its recognition by the algorithm for tape analysis and after having been evaluated by the investigator, and the total number of normal-to-normal beat intervals is determined. The mean heart period and heart rate variability (standard deviation of all normal RR intervals) are computed.

Implantable cardioverter-defibrillator - cardiac resynchronization therapy arrhythmia monitoring. In the subgroup of patients with an ICD or CRT, continuous electrogram monitoring will be available for the detection of malignant ventricular arrhythmias defined as VF or VTs with a heart rate > 150 b/min and a duration > 10 s.

Quality of life. The Minnesota Living with HF© survey tool is being used to assess the patient's perception of how his or her HF and therapy affect his or her life. The survey tool is designed as a simple, one page, self-administered questionnaire that has been validated in a number of HF studies. Twenty-one questions focus on the physical, socio-economic and psychological impairments that persons with HF frequently attribute to their condition.

A baseline measurement is taken at enrollment and at every subsequent follow-up examination in all patients.

Cardiopulmonary exercise testing. Cardiopulmonary exercise testing using a treadmill (or bicycle, see TWA measurements paragraph above) is performed at enrollment in all patients. It is repeated at 6 and 12 months of follow-up only in patients implanted with a resynchronization device. Instantaneous expiratory gas concentrations (O_2 uptake and CO_2 output) throughout the respiratory cycle and for 1 min of ventilation are measured continuously on a breath-by-breath basis. The peak O_2 is defined as the highest 30 s average of O_2 uptake during the last minute of exercise. The heart rate and blood pressure are measured at rest, during each stage of exercise, and at peak exercise using a sphygmomanometer.

Steering committee

The committee is responsible for developing and monitoring the implementation of the protocol. The

committee is supported by an independent statistician and is responsible for ensuring timely publication of the results.

Plan for statistical analysis

Descriptive statistics will be used to summarize the data collected in the clinical study. For discrete variables (e.g., gender, NYHA class), absolute and relative (%) frequencies will be reported. For continuous variables (e.g., patient age), means, standard deviations and ranges will be computed, unless in the presence of a skewed distribution (e.g. time), in which case median and quartiles will be calculated. The distribution of variables in the two study groups (TWA positive and negative) will be similarly summarized.

Primary endpoint. The prognostic role of TWA for predicting events during the 18 months of follow-up will be assessed by means of a Cox model. The relative risk of events in TWA positive with respect to TWA negative patients will be measured by calculating the hazard ratio, together with its 95% confidence interval. In order to refine these estimates and to assess the independent and additional prognostic effect of TWA, possible confounding factors will be included in the model. The known risk factors for the chosen outcome that will be considered are: age, NYHA class, left ventricular ejection fraction and maximum O_2 consumption. Alternatively, continuous variables will be dichotomized according to the median of their distribution and the model will be refitted. The calibration and discrimination of the model will be estimated to assess the model validity.

Secondary endpoints. The prognostic role of TWA on the time-to-death or time-to-event as defined in the secondary endpoints will be modeled by Cox regression. Event rate per person-months will be computed in TWA positive and TWA negative patients.

The hospitalization rate in the two TWA groups will be compared using models for counts (Poisson model or negative binomial regression in case of over-dispersion). The total length of hospitalization (as a proportion of the total observation time) in the two groups will be compared using the Mann-Whitney U test. The causes of hospitalization by TWA group will be compared using the Fisher exact test.

The McNemar test will be used to compare proportions of TWA positive at baseline and after 12 months in the CRT implanted population. Functional parameters deriving from the cardiopulmonary exercise examination and echo as well as the Minnesota questionnaire scores will be compared between baseline and 12 months using the Wilcoxon-matched paired test in the CRT implanted population.

No data imputation for missing values will be performed.

Timelines

The first patient was enrolled in June 2001. Recruitment is expected to be completed by mid 2004 and the study will report in 2006.

Addendum

After the arrival of the galley proofs the ALPHA study was completed. A total of 445 patients was enrolled.

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List of centers and relative physicians

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