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Rationale, Design, Implementation, and Baseline Characteristics of Patients in the DIG Trial: A Large, Simple, Long-Term Trial to Evaluate the Effect of Digitalis on Mortality in Heart Failure

The Digitalis Investigation Group

ABSTRACT: This article provides a detailed overview of the rationale for key aspects of the protocol of the Digitalis Investigation Group (DIG) trial. It also highlights unusual aspects of the study implementation and the baseline characteristics. The DIG trial is a large, simple, international placebo-controlled trial whose primary objective is to determine the effect of digoxin on all cause mortality in patients with clinical heart failure who are in sinus rhythm and whose ejection fraction is ≤ 0.45. An ancillary study examines the effect in those with an ejection fraction > 0.45. Key aspects of the trial include the simplicity of the design, broad eligibility criteria, essential data collection, and inclusion of various types of centers. A total of 302 centers in the United States and Canada enrolled 7788 patients between February 1991 and September 1993. Follow-up continued until December 1995 with the results available in Spring 1996. *Controlled Clin Trials 1996; 17:77–97*

KEY WORDS: *Design, large simple trial, randomized clinical trial, digoxin, heart failure*

INTRODUCTION

Congestive heart failure (CHF) continues to be a major public health problem in the United States, Canada, and other Western countries. The incidence and prevalence have been increasing in recent years despite significant advances in the prevention and treatment of cardiovascular diseases [1]. An aging population, control of other potentially lethal diseases, and increased survival from coronary heart disease (especially myocardial infarction) have all contributed to this increase in CHF. In the United States, the number of deaths in which CHF was considered to be the underlying or contributing cause increased from 118,000 in 1970 to 270,000 in 1990 [2]. The Framingham Heart Study recently reported an overall 5-year survival of 35% in men and 53% in women who were alive 90 days or more after the diagnosis of CHF [3]. In 1991, CHF was the primary discharge diagnosis for about 787,000 hospitalizations and was the leading "diagnostic-related group"

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Received May 6, 1994; revised January 11, 1995.

Controlled Clinical Trials 17:77–97 (1996)
Published by Elsevier Science Inc. 1996
655 Avenue of the Americas, New York, NY 10010

0197-2456/96/$15.00
SSDI 0197-2456(95)00065-O

(DRG) among hospitalized patients over 65 years of age [4]. Additionally, the National Heart, Lung, and Blood Institute (NHLBI) estimated the cost directly related to CHF hospitalization at over U.S. $6.9 billion.

For over 200 years, digitalis (digoxin) has been used to treat CHF. It is one of the most commonly prescribed drugs in the United States and in 1990 accounted for over 21 million prescriptions [5]. Approximately 70% of CHF patients are regularly prescribed digoxin, and although newer treatments, particularly angiotensin converting enzyme inhibitors (ACE-I), are now available for CHF, there has been little decline in the drug's use over the past 5 years (personal communication, Burroughs Wellcome 1989).

Despite the widespread use of digoxin, controversy exists regarding its role and its value in treating CHF patients in sinus rhythm. A survey of over 2700 physicians reported that approximately two-thirds of the physicians believed digoxin was effective in improving exercise tolerance, but less than one third thought that it prolonged life [6]. Obviously, if digoxin had a major impact on survival, the effect would have been detected by simple clinical observations, database studies, epidemiologic studies, and/or registries. It is more likely that any effect of digoxin on mortality and morbidity, either beneficial or deleterious, is only moderate, i.e., in the range of 10–20%. However, because CHF is a growing problem even a moderate reduction or increase in mortality would have a substantial medical and public health impact. Conversely, in the light of the arrhythmic potential of digoxin, the possibility of an adverse effect on survival needs to be examined.

In order to detect a moderate effect, a randomized trial of 7000–8000 patients with CHF is required [7]. Such a large study can be conducted at a reasonable cost only through wide collaboration among a large number of investigators from a wide variety of settings, including academic and community hospitals. In turn, to be practical in these various settings, the trial has to be simple in design with broad entry criteria and minimal data collection to enable incorporation of the trial procedures into routine clinical practice [8]. Simplicity in design and data collection would also facilitate screening and recruitment.

A fundamental principle of the large simple trial is to focus only on data or procedures that are essential to the main question. These include unbiased treatment allocation by proper randomization, important baseline patient descriptors and prognostic factors, assessment of adherence, elicitation of major and troublesome side effects only, use of relevant concomitant medications, and a well-defined hypothesis relying on an unbiased and complete evaluation of major clinical outcome measures such as death and hospitalization [9]. The participation of a wide group of physicians and broad entry criteria increases the feasibility of enrolling a clinically representative patient population and enables generalization of the trial results to a broad group of CHF patients. It also allows examination of a variety of subgroup effects using appropriate statistical methods.

A large simple trial evaluating the effects of digoxin on mortality in patients with CHF is feasible because the disease is common, the question is important, the drug is frequently used, and major clinical outcomes are easily documented. This article provides a detailed overview of the rationale behind key aspects of the design, implementation, and baseline characteristics of the Digitalis Investigation Group (DIG) trial, a large simple trial in CHF.

BRIEF HISTORY OF THE PLANNING PHASE

The NHLBI and the Department of Veterans Affairs Cooperative Studies Program (VACSP) agreed to collaborate in conducting the study because of (1) interest in the trial and expertise of the VACSP, (2) the accessibility of a large number of VA hospitals throughout the United States, and (3) reduction in the cost of trial due to the contribution of time and effort of certain staff personnel at the VACSP. The protocol was developed largely by a Core Group of the Digitalis Planning Committee (Appendix 1) and reviewed by external expert review committees at NHLBI and VACSP.

The most difficult issue to resolve was whether a large simple trial was both appropriate and adequate for evaluating treatments in patients with complex conditions such as CHF. After reviewing the International Study of Infarct Survival (ISIS) and Gruppo Italiano per lo Studio della Streptochinasi nell' Infarcto Miocardio (GISSI) series of trials in acute myocardial infarction [10–13] as well as the prevention and treatment trials of the Studies of Left Ventricular Dysfunction (SOLVD) [14], all of which incorporated many of the key concepts of the large simple trial methodology, the Core Group felt that a large simple trial was appropriate. However, it was decided that it would be important to have a well-described and defined protocol and to conduct an internal pilot phase monitored by the Data and Safety Monitoring Board (DSMB).

During protocol development, the planning and review committees discussed eight primary design issues extensively. The following is a summary of each issue along with the rationale for the final decision.

1. *Baseline clinical characteristics.* It is often assumed that one of the major limitations of large simple trials is that the minimal amount of data collection, particularly at baseline, might be insufficient to answer important questions or resolve unforeseen issues arising after the end of data collection for the trial [15]. In this trial in which mortality and morbidity are the endpoints, it was decided that data collection could be limited to important prognostic determinants and variables that might modify the effects of therapy. Essential and key clinical descriptors of heart failure would also be collected so that the results of the trial can be applied to clinical practice. Thus, it was agreed that participants would be characterized by age, gender, etiology, severity based on New York Heart Association (NYHA) functional class, ejection fraction (EF), and any concomitant treatment known to interact with digoxin.
2. *Stratification of the treatment groups.* Stratification prior to randomization is used to assure an adequate representation of important baseline characteristics such as NYHA class and EF in each of the treatment groups. However, in large trials, stratification has little advantage over stratified analyses and adds considerably to the complexity of conducting the trial with hindrances such as the necessity for maintaining a larger drug supply, making extra steps for investigators, and incurring extra costs due to wasted drugs. Given the large sample size, there was no reason to expect uneven distribution within the various subgroups of interest. Although the Core Group decided to only stratify by center, sufficient baseline data were to be collected to allow retrospectively stratified analyses. Five prespecified subgroups (etiology,

previous use of digoxin, NYHA class, EF, and heart size) were identified for secondary analyses.

3. *Maintaining study blind and the potential effect on the interpretation if significant unblinding occurred.* The Core Group discussed whether or not to use a placebo with a double-blind approach or incorporate an open control group. It was generally felt that a blinded study would be preferable because this might reduce the potential for biases in the use of ancillary treatments and in the classification of secondary outcomes (e.g., causes of hospitalization) as well as minimize drop-ins (use of digoxin in the placebo group). Furthermore, a blinded trial was more likely to provide reliable answers on the incidence of digoxin toxicity.

   Although the trial was to be blinded in theory, there was a concern that investigators could be easily unblinded by obtaining serum digoxin levels. Because this potential problem could not be completely avoided, the group established a number of strategies to minimize this (e.g., reminders on chart labels and posters to avoid unblinding). It was emphasized that even if the patient's private physician were unblinded, attempts should be made to keep the study investigators and patient blinded. Furthermore, such patients would still be part of the study and included in the final analysis.
4. *Accurate and consistent assessment of EF at baseline.* Because EF is a powerful predictor of mortality, careful consideration was given to its assessment. The three methods used to measure EF are radionuclide angiography, contrast angiography, and two-dimensional (2-D) echocardiography. Although the Core Group considered radionuclide and contrast angiography to be the most accurate methods, there were several factors in favor of allowing centers to use any of the three methods described previously. First, data from the SOLVD trials showed that each method gave similar prognostic information on the relation between EF and mortality (SOLVD, unpublished data). Second, in the DIG trial EF is used to divide patients into prognostically different categories and is not used as an endpoint. Third, many of the potential centers in nonacademic settings may not have access to either of the angiographic methods, which would increase the difficulty of recruiting a sufficient number of participating centers. Fourth, EF measured by any of the methods reflects usual clinical practice. Fifth, there would be substantial cost savings in allowing the use of any of the three methods. Therefore, the protocol allowed measurement of EF within 6 months of randomization using any of the three techniques when there had been no intercurrent cardiac event.
5. *Use of concomitant drugs confounding trial results.* During the planning phase, there was concern regarding the use of concomitant drugs, particularly ACE-I, and the potential risk of early imbalance in cotherapy. Although ACE-I therapy was likely to be used, it was difficult to adopt a definitive policy before the results of the V-HeFT-II and SOLVD treatment trials were made publicly available [16,17]. However, it was finally concluded that the DIG study should strongly recommend that all participants with an EF $\leq$ 0.45 be on an ACE-I unless there were known contraindications or intolerance. It was also decided that the use of other drugs for CHF, such as diuretics, should be left to the investigator and not mandated by the protocol.

Data on the use of a limited number of relevant concomitant medications were to be collected at each visit.

6. *Randomization of patients previously on digoxin and placebo run-in period for all patients prior to randomization.* There was concern that early deterioration and withdrawal of patients previously on digoxin who would be randomized to placebo would lead to increased dropouts and consequent loss of statistical power. However, it was also considered important to include patients previously on digoxin because excluding them may lead to selection of a "healthier" patient population with a low event rate. Additionally, patients both on digoxin and not on digoxin should be included to expand the generalizability of the study results. The potential use of nonstudy digoxin could be minimized by requiring that patients be stable at the time of randomization and optimizing other CHF treatments such as the use of diuretics and ACE-I. A large sample size would maintain the power to detect differences even if some patients in the placebo group received nonstudy digoxin. Thus it was decided to randomize patients in the trial regardless of whether or not they had previously used digoxin. The Core Group decided that it would be best not to have a digoxin withdrawal period. The protocol stated that patients currently on digoxin and who had been stable for at least 2 weeks, unless otherwise ineligible, could be randomized immediately.
7. *Monitoring of serum digoxin levels for both therapeutic reasons and patient safety in a blinded trial.* The Core Group considered carefully the extent to which the monitoring of digoxin would be necessary to maintain dosage within the therapeutic range and to minimize toxicity. Because high serum digoxin levels without clinical signs of toxicity do not prove toxicity, the Core Group felt that the value of the test was primarily to confirm toxicity in patients with a clinical suspicion. Conversely, a proportion of patients with true toxicity have serum digoxin levels in the normal range. In spite of a weak correlation between serum digoxin levels and toxicity, it was decided that serum digoxin levels would be obtained at 4-week and 12-month visits on the first 1000 patients and assessed blindly at a central laboratory. After reviewing the levels on these patients, the DSMB would decide whether to continue serum digoxin levels on all patients. The results would be used to monitor for safety and to establish that the digoxin dosage schedule and the serum digoxin levels were within the therapeutic range. In addition, investigators were urged not to obtain serum digoxin levels at a local laboratory. Instead they were requested to send blood samples for suspected digoxin toxicity to the central laboratory, which would provide the results within 48 hr.
8. *EF entry criteria.* Another area of extensive discussion was whether or not to include patients with CHF and preserved systolic function. There were concerns that if there were no EF entry criterion, then the proportion of patients with low EF may not be sufficient to maintain statistical power. However, there were also compelling reasons to include patients with a preserved EF. First, because digoxin inhibits neurohormonal and sympathetic nervous system response and enhances vagal effects, it may be beneficial in patients with only moderate or limited systolic impairment. Second, the relationship between EF and clinical response to digoxin is unknown. Third, if the benefits of digoxin are independent of EF, then study results

Table 1 List of Exclusion Criteria

1. Age < 21 years
2. Baseline left ventricular EF not available
3. Myocardial infarction, cardiac surgery, or percutaneous transluminal coronary angioplasty (PTCA) within 4 weeks
4. Unstable or refractory angina < 1 month
5. II°–III° AV block without a pacemaker
6. Atrial fibrillation (with or without pacemaker) or atrial flutter
7. Cor pulmonale
8. Constrictive pericarditis (such patients are eligible after surgery)
9. Acute myocarditis
10. Hypertrophic cardiomyopathy
11. Amyloid cardiomyopathy
12. Complex congenital heart disease
13. Pre-excitation syndromes
14. Current treatment with intravenous inotropic agents
15. Potassium below 3.2 mmol/L or above 5.5 mmol/L
16. Need for cardiac surgery (e.g., severe valvular disease, planned coronary artery bypass graft surgery) or PTCA in the near future. (Such patients are eligible after surgery or PTCA.)
17. Patients on heart transplant list are not eligible
18. Sick sinus syndrome without pacemaker
19. Recognizable noncardiac causes of CHF
20. Significant renal insufficiency (creatinine > 3.0 mg/dL) or severe liver disease. Any noncardiac disease that shortens life expectance to less than 3 years (e.g., most cancers)
21. Patient is unlikely to comply with the protocol requirements for follow-up and drug adherence (e.g., chronic alcoholism, no fixed address)

can be applied more broadly without the need to measure EF before initiating treatment. Therefore, the study planned to include patients with EF $\leq$ 0.45 in the main trial and conduct a separate ancillary study of patients with EF > 0.45.

STUDY DESIGN

Objectives

The primary objective is to determine the effect of digoxin on mortality of all causes in patients with clinical heart failure who are in sinus rhythm and whose EF $\leq$ 0.45. *The secondary objectives* are to determine (1) if digoxin reduces hospitalization for worsening heart failure, as well as to (2) evaluate the efficacy of treatment on cardiovascular mortality, (3) deaths due to progressive heart failure, (4) hospitalizations for all other causes, including digoxin toxicity, and (5) death and hospitalization for CHF in patients with EF > 0.45.

The efficacy of digoxin treatment on mortality in subgroups will be assessed by EF, heart size on chest X ray, etiology, previous digoxin use, and NYHA functional class. The effect of digoxin on mortality is expected to be greater in the first 2 years after randomization. Therefore, mortality and hospitalization for CHF that occur within this period will be analyzed separately as secondary endpoints.

Table 2 Range of Study Size Under a Number of Assumptions

Common assumptions for all calculations:

1. Option A: Placebo drop-ins, 15% over 3 years (5% per year); digoxin dropouts, 15% over 3 years (5% per year)
2. Option B: 5% dropouts/drop-ins the first month, then 5% in the remaining 11 months and each subsequent year (total of 20% at the end of the study)

Three-Year Mortality Rate (Options)	Hypothesized Percentage Reduction in Mortality[a]	
	15%	20%
27% (A)	6700 (13%)	3700 (17%)
(B)	7500 (12%)	4100 (16%)
30% (A)	5800 (13%)	3200 (17%)
(B)	6500 (12%)	3600 (16%)

[a]Observed risk reductions are in parentheses.

Based on 90% power to detect a 15–20% reduction in mortality using a two-tailed α of 0.05.

Study Participants

The diagnosis of CHF is based on current or past evidence of low cardiac output (such as limitation of activity or fatigue) or congestion edema, elevated jugular venous pressure (JVP), or rales or cardiologic evidence of pulmonary congestion. EF is assessed by one of the following techniques: (1) radionuclide left ventricular angiography, (2) left ventricular contrast angiography, or (3) 2-D echocardiography. EF measurements and chest X rays within 6 months before randomization are accepted if no major cardiac event such as myocardial infarction or cardiac surgery occurred between the time of measurement and randomization. If EF has been measured several times or by more than one technique within a short period of time, the protocol recommends using the most recent EF. An EF measured within 7 days of an acute cardiac event or surgery cannot be used.

Table 1 lists the exclusion criteria. The DIG study has no upper age limit and actively encourages the enrollment of the elderly, women [18–20], and minorities to have as representative a sample of the total CHF patient population as is feasible.

Study Sample Size and Power

In the Coronary Artery Surgery Study registry data, 3-year mortality rates of 40–45% were observed among CHF patients not receiving vasodilator therapy (CASS Registry, unpublished data). ACE-I have been reported to reduce this mortality rate by an estimated 16–20% [21,22]. Because most of the patients in the DIG study would be receiving an ACE-I and participants in clinical trials often experience a lower than expected event rate, sample size was based on a projected 3-year mortality rate of 27–30%.

Taking noncompliance into account, the main study would need to enroll at least 7000 patients with an EF $\leq$ 0.45 to have 90% power to detect a 12% reduction in mortality by treatment (Table 2) [23]. For the ancillary study of patients with an EF $>$ 0.45, 1000 patients need to be accrued to have 80% power to detect a 30% reduction in the combined endpoint of hospitalization for CHF and death.

It was estimated that with a minimum of 200 participating centers, 3 years would be required to recruit the projected numbers of patients. Follow-up of patients would be for a minimum of 2 years; hence, the study would last for a maximum of 5 years.

Statistical Analysis

For mortality, the primary endpoint, survival distributions will be estimated using the Kaplan–Meier method [24] and compared using the log-rank statistic [25] at the 0.05 level. For the five secondary endpoints, after adjusting for multiplicity, the overall test will be performed at the 0.01 level.

The specified subgroup hypotheses for both the primary and secondary endpoints will be examined by tests of interactions. The five tests of interaction on mortality will be performed at the 0.05 level. If a test of interaction is significant, the treatment effects will be described utilizing odds ratios and their 95% confidence intervals. The relationship between EF and effect size will be analyzed utilizing regression techniques.

No p values will be assigned for data-derived subgroups for primary or secondary endpoints.

Data Monitoring Guidelines

The DSMB is monitoring the data about every 6 months. Formal statistical guidelines are symmetric and based on the primary endpoint but the DSMB looks at all endpoints of interest. The DSMB agreed to monitor with a nominal Z of 4 for the first half of the trial, a nominal Z of 3 for the second half, and a nominal Z of 2 remaining for the final analysis.

Ethics and Informed Consent

Because many of the participating centers are community hospitals or private practices without access to Institutional Review Boards (IRBs), a number of mechanisms were incorporated to ensure protection of patients' rights. A university or a central IRB ("umbrella" IRB) was available to act on behalf of the centers without access to a local IRB. All centers had to obtain approval from the Office of Protection from Research Risks (OPRR) at the National Institutes of Health.

Patients Receiving Previous Digoxin Therapy and Stabilization Phase

Eligible patients currently on digoxin and an ACE-I and who are stable for at least 2 weeks are immediately randomized to digoxin or placebo. Patients not on an ACE-I are prescribed a drug from this class and are seen 2 weeks later. Other treatments such as a low-salt diet, increased physical activity, use of diuretics and other therapy for CHF are optimized. Then patients who are clinically stable are randomized as above. This phase attempts to minimize the number of patients who require open-label digoxin after randomization.

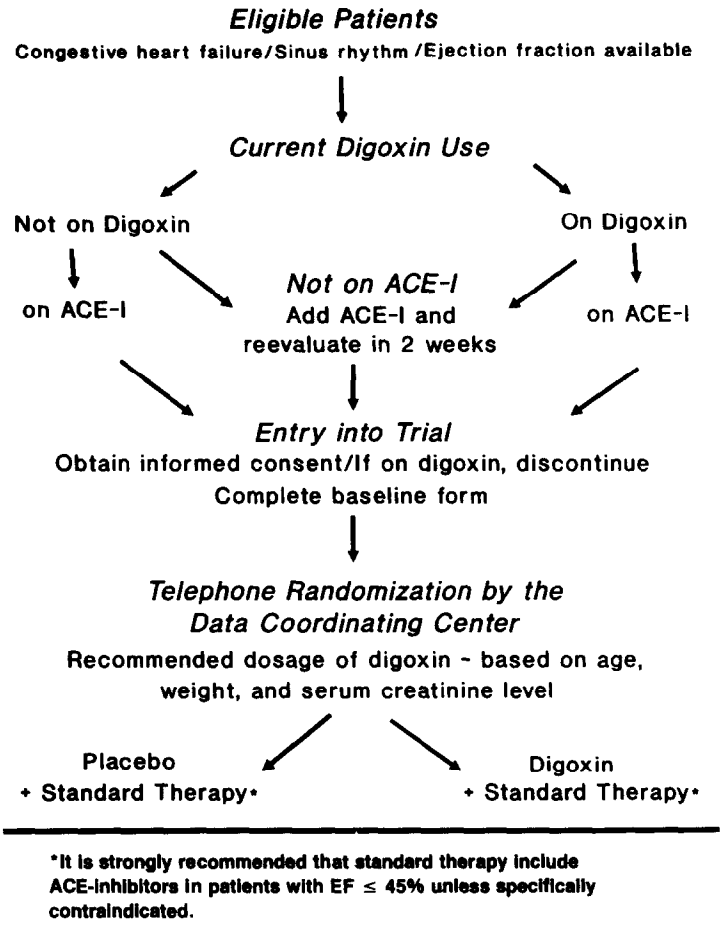

Figure 1 Randomization scheme.

Telephone Randomization Procedures and Dose Algorithm

Figure 1 shows the randomization procedures for all patients found to be eligible at entry into the main and ancillary study. Investigators enroll patients by calling a toll-free number to confirm eligibility and to receive a recommended dosage of digoxin based on age, gender, weight, and renal function [26]. The investigator may prescribe a different dosage based on other factors such as previous digoxin dosage and use of concomitant drugs that might interfere with digoxin levels. Participants are allocated to either digoxin or placebo using a random block size method within each clinical center. The study medications are packaged so that the dosage can be adjusted as needed. To ensure that key baseline data are complete on all patients, some of the data are collected at the time of randomization whereas the remaining data are completed on a simple two-page baseline form.

Follow-Up Visits

The first follow-up visit is scheduled for 4 weeks after randomization and then at 4-month intervals thereafter until the end of the study. At each visit, a follow-up

Table 3 Summary of DIG Substudies

Substudy	Study Schedules					Number of Participating Centers	Number of Participants[a]
	Baseline	1 week	4 weeks	4 mo	12 mo		
Quality of life	+		+	+	+	39	581
Six-minute walk test	+		+	+	+	39	547
Holter	+			+		45	540
SAECG[b]	+			+		45	287
Neurohormonal	+	+		+	+	6	55

[a]The participants are not necessary in all the substudies.

[b]SAECG = signal averaging electrocardiogram.

form is completed and mailed to the Data Coordinating Center (DCC). At the 4-week and 12-month visit, a blood sample is sent to the central laboratory to determine the routine serum digoxin level.

At each visit adherence is assessed by determining the number of tablets returned using either the calibrated graduated cylinder or the actual tablet count. Because each bottle contains the maximum amount of study medication regardless of the dose, the cylinder along with a chart that converts millimeters to an approximate number of tablets was developed to estimate quickly the number of returned pills in bottles without laborious tablet counting.

Unblinding/Suspected Digoxin Toxicity

Every effort is taken to avoid unblinding. Obtaining serum digoxin levels at a local laboratory is strongly discouraged, except for life-threatening situations. If a serum digoxin level is essential, the investigators are requested to send a blood sample to the central laboratory. The results are reported as one of three levels (i.e., subtherapeutic, therapeutic or possibly toxic, and probably toxic) within 48 hr. Patients in the placebo group are reported to have a subtherapeutic serum level of digoxin.

Substudies

The number of substudies conducted is limited in order to prevent undue additional burdens and complexity. Thus, the centers had the option of participating in the various substudies. The substudies being conducted among a different subset of patients are (1) quality of life/6-minute walk test substudy, (2) holter/signal averaging electrocardiogram (SAECG) substudy, and (3) neurohormonal substudy. Table 3 presents a brief summary of the substudies. The aim of the quality of life and 6-minute walk test substudy is to determine the effect of treatment on a patient's well-being, daily activities, and functional status. The main objective of the holter/SAECG substudy is to examine the pathophysiology of sudden cardiac death. The primary objective of the neurohormonal substudy is to determine whether long-term administration of digoxin attenuates the neuroendocrine response in patients with heart failure.

Table 4 Characterization of Participating Investigators and Center Specialty (%)

Type of Practice	Cardiovascular (N = 229)	Noncardiovascular[a] (N = 73)
University and university-affiliated	39	14
Office	25	49
Veterans Administration	18	19
Other community	18	18

[a]Includes internal medicine, geriatrics, family practice, and general practice.

Data Quality Assurance

The data are entered and verified within 2 weeks of receipt at the DCC and edited biweekly. The data edit rates, except for the event and 6-minute walk data forms, as well as the total error rate are under 1%. The quality of the data collected is confirmed by regular editing and random site visits that include review and verification of specified entry and baseline criteria.

ORGANIZATIONAL STRUCTURE

There were two unique aspects of this trial's organization. First the 302 participating clinical centers are distributed throughout the United States and Canada. The centers range from university, research, and community hospitals to group practices and private individual physicians. Table 4 summarizes the characteristics of the participating centers. Second, four geographically distributed regional coordinating centers in Canada assist in recruitment, monitoring, and support for the Canadian centers. Similar to other large trials, a steering committee, a DSMB, a DCC, and a Pharmacy Coordinating Center ensure that the study is performed efficiently.

INITIATING THE DIG STUDY

Because DIG is a large simple trial, a brief 35-page protocol including three short (one or two pages) data forms (baseline, follow-up, and event forms) were developed to allow easy incorporation of the trial into the usual clinical practice for treatment of patients with CHF.

In order to recruit an adequate number of clinical centers, a letter of invitation along with a copy of the protocol was sent to the cardiology departments of every hospital in the United States and Canada, to members of the American College of Cardiology, and to investigators who had participated in ISIS, SOLVD, the Cardiac Arrhythmia Suppression Trial, and other NHLBI-sponsored clinical trials. Family practice networks (Ambulatory Sentinel Practice Network and Wisconsin Research Network) were also approached. Several national and regional meetings were held in the United States and Canada to recruit and train prospective participating investigators.

In order to assist the investigators in performing the study more efficiently, a number of study aids were developed, packaged in a briefcase, and provided to each participating center. The standard study aids include patient and physician

information brochures, patient identification cards, and chart labels. The unique study aids include pocket protocols, a study video and slides, and an adherence cylinder. A summary of the protocol appears on a laminated card that fits into a pocket and includes the eligibility and exclusion criteria, randomization flow chart, and follow-up schedule. The study video and slides provide an overview of the study and procedures that can be shared with potentially interested colleagues. The calibrated graduated cylinder and chart provide a quick method to assess adherence.

IMPLEMENTATION OF THE DIG TRIAL

A total of 354 centers obtained local IRB and OPRR approval. Prior to randomization of their first patient, 52 sites withdrew from the study because of perceived inability to recruit and follow up at least 36 patients. Among the remaining 302 centers, 186 are in the United States and 116 are in Canada.

Table 5 shows that the baseline characteristics of the study population are well balanced by treatment group. The mean age of the patients is 63.9 years; about 28% are over 70 years old, 25% are women, and 85% are white; the mean EF is 32% with 13% having an EF > 0.45. Although the majority of participants have mild to moderate heart failure based on NYHA class (II and III), 81% of participants have four or more symptoms of CHF. About 43% of the patients had previously used digoxin. A large majority are on diuretics (86%) and/or ACE-I (93%) therapy. Ischemic heart disease is the primary etiology of CHF (70%) followed by idiopathic dilated cardiomyopathy (14%) and hypertensive heart disease (10%).

DISCUSSION

The DIG study was designed as a large, simple trial because of (1) the importance of detecting even a moderate impact of digoxin in a representative sample of the CHF population, (2) the large sample size requirement, and (3) the need to minimize costs. In cardiovascular diseases, a number of large simple trials have been successfully completed, e.g., the ISIS trial [10–12], the GISSI trial [13], and the GUSTO trial [27]. These trials evaluated an acute intervention in a well-defined population admitted to a specific setting (coronary care unit) with a short follow-up period. By contrast, the DIG study is evaluating a long-term intervention in a less well-defined chronic disorder with multiple complications. These factors could affect patient adherence to the protocol.

In order to implement and complete the DIG study, a number of issues have been addressed. The first is the recruitment of a large number of dedicated clinicians who would be willing to participate with a modest level of funding that would only cover the "costs" related to completion of study forms and specific medical procedures. It is primarily the recognition of the importance of the question that attracted over 300 clinicians to participate with such modest reimbursement. In addition, the experience of the DIG study has been consistent with the expectation that busy practitioners could successfully participate in a trial of an important question as long as the entry criteria were kept broad.

A second issue is the simple design of the study. The DIG study has a short, simple protocol with only three short data forms, follow-up procedures similar

Table 5 Baseline Characteristics of the DIG Cohort by Treatment Group

Characteristic	Placebo (N = 3899)	Digoxin (N = 3889)
	Mean ± SD	
Age (years)	64.0 ± 10.8	63.8 ± 11.0
Ejection fraction	31.9 ± 12.5	32.0 ± 12.5
	Median	
Duration of CHF (months)	16	17
	Percentage	
Gender (female)	24.7	24.7
Race (nonwhite)[a]	14.6	14.3
EF (> 45%)	12.7	12.6
Age (> 70 years)	28.6	28.0
EF method		
Radionuclide	64.6	65.7
2-D echocardiogram	29.6	29.0
Contrast angiography	5.7	5.3
CT ratio (> 0.50)	60.4	60.0
NYHA class		
I	14.0	14.4
II	54.8	54.1
III	29.3	29.5
IV	1.9	2.0
Number of symptoms of CHF		
1	2.1	2.2
2	7.1	7.1
3	8.9	9.2
4+	80.9	80.5
Medical history		
Previous MI	63.3	62.8
Current angina	26.8	27.5
Diabetes	28.8	28.2
Hypertension	47.2	47.1
Previous digoxin use	43.6	42.8
Concomitant medications		
Diuretics	82.1	80.9
ACE inhibitor	93.7	93.1
Nitrates	42.1	41.5
Other vasodilators	17.0	15.4
Primary etiology		
Ischemic	68.7	69.1
Idiopathic	13.3	14.2
Hypertensive	10.6	10.0
Valvular	2.4	2.0
Alcohol-related	3.5	2.5
Other	1.2	2.0

[a] Includes blacks and other.

to those used in the usual clinical setting, toll-free phone numbers for randomization and questions, a number of study aids such as a pocket protocol, preaddressed stamped envelopes, laboratory supplies and shipping for all blood samples, and individual patient kits for study medication.

A third issue is adequate logistic and information support and advice for the investigators. The Project Office is available to address medical problems and

questions; the DCC provides administrative, budgetary, regulatory, and data management support; and the Pharmacy Coordinating Center provides the drug supply and is available 24 hours a day for emergency unblinding. The regional Canadian coordinating centers provide specialized support to the Canadian investigators. A central laboratory performs both routine and emergency serum digoxin levels. In addition, each center is provided a number of study aids in order to simplify the study performance.

The final issue is the ability to maintain the interest and boost the morale of the investigators and patients over the entire course of the study. Regularly scheduled study group meetings are held to maintain an interest in the trial. In addition to reviewing study progress and discussing study problems, a portion of these meetings is devoted to a scientific, educational program providing continuing medical education credits. A study newsletter that highlights study progress, discusses protocol issues, gives answers to commonly asked questions, and provides other items of interest is sent to investigators on a regular basis. In addition, a patient newsletter that contains articles on study progress and cardiovascular disease is distributed.

A large number of dedicated DIG investigators have successfully recruited 7788 patients 4 months ahead of schedule and follow-up has proceeded well over the first 30 months of the study. Although the centers provided generally good-quality data, editing of data forms and verification of data during the random site visits has resulted in a high-quality data base. Participants will be followed through 1995 with the results expected to be published in early 1996.

APPENDIX

A great many people have contributed to DIG. The following list of principal investigators, coordinators, and members of committees presents the affiliations of each person only once. Principal investigators without listed affiliations are in private practice. Abbreviations used: U = University; Med = Medical; Hosp/Hop = Hospital; HSC = Health Science Center; Gen = General; Coord = Coordinating; Coop = Cooperative; Instit = Institute; Ctr = Center; NHLBI = National Heart, Lung and Blood Institute; VAMC = VA Medical Center.

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REFERENCES

1. Kannel WB, Belanger AJ: Epidemiology of heart failure. Am Heart J 121:951–957, 1991
2. National Center for Health Statistics: Public use data tapes from Division of Vital Statistics, 1970 and 1990
3. Ho KK, Pinsky JL, Kannel WB, Levy D: The epidemiology of heart failure: the Framingham Study. J Am Coll Cardiol (Suppl A)22(4):6A–14A, 1993
4. Graves EG: National Discharge Survey, Annual Summary 1991, National Center for Health Statistics. Vital Health Stat 13:114, 1993
5. National Disease and Therapeutic Index. Plymouth, PA: IMS America Pharmaceutical Database 3 (June–Dec):2289, 1990
6. Hlatky MA, Fleg JL, Hinton PC, et al: Physician practice in the management of congestive heart failure. J Am Coll Cardiol 8:966–970, 1986
7. Furberg CD, Yusuf S, Thom TJ: Potential for altering the natural history of congestive heart failure: need for a large clinical trial. Am J Cardiol 55:45A–47A, 1985
8. Yusuf S, Held P, Teo K, Toretsky ER: Selection of patients for randomized controlled trials: implications of wide or narrow eligibility criteria. Stat Med 9:73–86, 1990
9. Yusuf S, Collins R, Peto R: Why do we need some large, simple randomized trials? Stat Med 3:409–420, 1984
10. ISIS-1 Collaborative Group: Randomized trial of intravenous atenolol among 16,027 cases of suspected acute myocardial infarction. Lancet 2:57–66, 1986
11. ISIS-2 Collaborative Group: Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. Lancet 13:349–360, 1988
12. ISIS-3 Collaborative Group: A randomized comparison of streptokinase vs. tissue plasminogen activator vs. anistreplase and of aspirin plus heparin vs. aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 339:753–770, 1992
13. Maggioni AP, Franzosi M, Farina ML, Santoro E, Celani M, Ricci S, Tognoni G: Cerebrovascular events after myocardial infarction: analysis of the GISSI trial. Br Med J 302:1428–1431, 1991
14. The SOLVD Investigators: Studies of left ventricular dysfunction (SOLVD) – rationale, design and methods: two trials that evaluate the effect of enalapril in patients with reduced ejection fraction. Am J Cardiol 66:315–322, 1990

15. Lubsen J, Tijssen JGP: Large trials with simple protocols: indications and contraindications. Controlled Clin Trials 10:151S–160S, 1989
16. Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M, et al: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 325:303–310, 1991
17. The SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 325:293–302, 1991
18. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from the clinical trials in acute myocardial infarction. JAMA 268:1417–1422, 1992
19. Douglas PC: Gender, cardiology and optimal medical care. Circulation 74(5):917–919, 1986
20. Yusuf S, Furberg CD: Are we biased in our approach to treating elderly patients with heart disease? Am J Cardiol 68:954–956, 1991
21. Cohn JN, Archibold DG, Zieche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a veterans administration cooperative study (V-HeFT). N Engl J Med 314:1547–1552, 1986
22. The CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 316:1429–1435, 1987
23. Wu M, Fisher M, DeMets DL: Sample size for long-term medical trials with time dependent noncompliance and event rates. Controlled Clin Trials 1:109–121, 1980
24. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958
25. Peto R, Pike MC, Armitage P, et al: Design and analysis of randomized clinical trials requiring prolonged observations of each patient: II. Analysis and examples. Br J Cancer 35:1–39, 1977
26. Jeliffe RW, Brooker GA: Nomogram for digoxin therapy. Am J Med 57:63, 1974
27. GUSTO Investigators: An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 392:673–683, 1993