Patient Comprehension and Reaction to Participating in a Double-blind Randomized Clinical Trial (ISIS-4) in Acute Myocardial Infarction

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Background: Although randomized clinical trials are currently the standard for the evaluation of new therapeutic strategies, little attention has been paid to the viewpoint of the patients recruited to these trials.

Objective: To examine the perspective of the Israeli patient cohort who participated in the Fourth International Study of Infarct Survival, a randomized trial in acute myocardial infarction.

Methods: A patient questionnaire was mailed to 360 Israeli patients who participated in the Fourth International Study of Infarct Survival and was returned by 150 of them. Main outcome measures included patient perception of consent procedures, comprehension of the study, subjective reaction to participating in the trial, and interest in present and future trials.

Results: Forty (31%) of 129 patients perceived that they had full comprehension of the trial, while 64 (50%) claimed partial understanding and 25 (19%), no understanding at all. Comprehension was related to a recollected explanation of 5 minutes or more ($P < .001$) and to an opportunity for discussion at the time of consent ($P < .001$). Most patients recollected the oral explanation; fewer, the written material. Patient consent was given by 64 (43%) of 150 patients in the hope of better treatment. In 36 cases (25%), the patients felt they received better treatment because of participation in the trial.

Conclusions: Despite proper attention to accepted ethical and legal standards, perceived patient comprehension in this trial in acute myocardial infarction was incomplete or lacking in a considerable number of subjects. Much progress must be made toward the goal of true informed consent in clinical trials.

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RANDOMIZED clinical trials are the criterion standard for evaluating new treatment modalities and are ethically justified. These trials expose the patient to state-of-the-art therapeutic strategies, but most trials dictate management decisions at randomization centers far from the patient and the attending physician, with an inevitable compromise in the traditional physician-patient relationship. Little attention has been paid to the perspective of the patients recruited to a trial, and particularly so in the circumstances of acute myocardial infarction.

The Fourth International Study of Infarct Survival (ISIS-4) was a large double-blind clinical study examining by factorial design the effect of captopril, nitrate, and magnesium in patients treated for acute myocardial infarction in 1086 hospitals in 31 countries. The study showed that captopril treatment, commenced within 24 hours of the acute event and continued for at least 1 month, reduced 35-day and 1-year mortality, whereas there was no long-term survival benefit associated with oral nitrate therapy or with magnesium. The ISIS-4 and other large clinical trials have directed and shaped the management of acute infarction so that hospital mortality has decreased to approximately 6% to 8% during the past decade.

The present study was undertaken to examine the patient viewpoint after participation in the ISIS-4 trial. We specifically examined the processes operating at the time of informed consent and the factors that determined patient willingness to participate in the trial. We questioned patients on their experiences during the study and analyzed factors that might play a role in their openness to participation in future clinical research projects. The information is highly relevant to the ethical and humanistic issues involved in the recruitment of patients to clinical trials in the acute medical situation.
PATIENTS AND METHODS

PATIENT POPULATION

The ISIS-4 study population included 58,050 patients thought to be within 24 hours of the onset of symptoms of suspected acute myocardial infarction. Contraindications to inclusion in the study were specified by the attending physician and included conditions such as persistent hypotension, cardiogenic shock, life-threatening disease, and very small infarction. The study was carried out under the rules and regulations of the Declaration of Helsinki regarding clinical research, with approval of the protocol by the institutional review board of each individual participating hospital and by the appropriate health authority according to legislation in each participating country. Entry to the study for Israeli patients was by free telephone to a central 24-hour randomization service in Oxford, England. Baseline details about the patient were submitted by telephone, and a computer program used a minimization algorithm when allocating a specific numbered trial treatment pack to each patient, which limited chance differences between the treatment groups regarding baseline features.

The present study was conducted in the Israeli population who participated in the ISIS-4 study. In accord with health care regulations for clinical trials in Israel, all patients signed an informed consent form on recruitment to the study. An oral explanation should have been given to each patient, as well as an internationally standardized written explanation of the ISIS-4 study, which was available in both Hebrew and English. Patients recruited to trials in Israel who are unfamiliar with these languages receive explanations via an interpreter, who is usually a member of the medical or paramedical staff of the hospital. The details of this process differ by center and also according to the clinical status of the patient, especially in the circumstances of acute myocardial infarction.

One to 3 months after the acute event, a questionnaire was mailed to 360 of the 428 patients recruited in 14 centers in Israel, excluding patients who had died and those with known difficulty in the language of the questionnaire (Hebrew). To ensure patient confidentiality and to promote patient cooperation and openness, the questionnaires were anonymous, and this was clarified in an accompanying letter to the patient. Fully or partially completed questionnaires were received in self-addressed return envelopes from 150 patients, and these form the basis of this report. To preserve the voluntary and open nature of the information submitted by patients, no attempts were made to coerce patient response by repeated mailings and telephone calls, which, because of the anonymity of the study, would have meant repeated pressure on responders as well as nonresponders.

PATIENT QUESTIONNAIRE

The patient questionnaire (Table 1) included 22 items related to 3 different periods of hospitalization: (1) explanation of the study and patient comprehension at the time of consent and randomization (questions 1-8), (2) feelings and reactions of the patient, family, and family practitioner during the study (questions 9-17), and (3) response and emotions of the patient after completion of the study (questions 18-22). The replies were analyzed by standard statistical tests of frequency distribution, correlation, and association tests. Incomplete responses to the questionnaire account for the differing total numbers of patients given for replies to individual questions.

RESULTS

EXPLANATION OF THE STUDY

All patients signed an informed consent form on recruitment to the study. Although all patients should have received an oral and written explanation as part of the process of informed consent (all received an explanatory document), only a third (36/113 [32%]) recalled both an oral and written explanation, 71 (63%) recalled the oral explanation, and 6 (5%) recalled only the written description of the project. The duration of the explanation was estimated by 49 (39%) of 126 patients to have lasted more than 5 minutes, 63 (50%) believed that the explanation was less than 5 minutes, and 14 (11%) did not recall any explanation. The explanation was thought to have been given by a physician in 77 (65%) of 119 patients, by a nurse in 6 (5%), and by both a physician and a nurse in 30 patients (25%). There was an opportunity to ask questions in 88 (59%) of 150 cases, no opportunity in 53 (35%), and no reply to this question in 9 (6%).

COMPREHENSION OF THE STUDY

Forty (31%) of 129 patients replied that they had a full comprehension of the study, 64 (50%) claimed partial comprehension, and 25 (19%) had little or no understanding at all (the remainder gave no reply) (Table 2). Comprehension of the study was related to the duration of explanation (P<.001), but not to the personnel explaining the study or to whether the explanation was oral or written. Patients who had an opportunity to ask questions had a better comprehension of the study than those who did not (P<.001).

The reasons for participating in the ISIS-4 study were as follows. Patient consent was given in 64 (43%) of cases because of the hopes of better treatment (46 [31%]) or follow-up (18 [12%]). Fifty-three patients (35%) were willing to participate with the expectation of helping and promoting medical research. In 21 patients (14%) there was no clear reason, and 12 (8%) replied that they were afraid to refuse when asked to join the study.

PATIENT REACTION DURING AND AFTER THE STUDY

In 36 cases (24%), the patients felt that they had received better medical treatment because of participation in the study. The medical treatment was not thought to have been better by 73 patients (49%), and 41 (27%) were uncertain. Possible psychological benefits of participating in ISIS-4 were reported as follows:
about one third of patients (54 [36%]) reported that the study gave them a feeling of greater security, 46 (31%) reported that participation gave them an interest in medical science, a quarter (35 [23%]) reported no particular feeling of benefit, and 15 (10%) had a variety of other reactions.

The possibility of placebo therapy was a cause for concern in 39 (28%) of 141 patients. The possibility of placebo was of little importance in 26 patients (18%) and of no importance at all in 76 (54%). There was no relationship between perceived comprehension of the study and the reaction to the possibility of placebo therapy.

**PATIENT ATTITUDE TO RESULTS OF THIS AND TO POSSIBLE FUTURE STUDIES**

Most patients (121/136 [89%]) expressed an interest in the results of the ISIS-4 study, 15 (11%) did not, and the others gave no response. Approximately half (60/121 [50%]) of the patients who claimed interest in the results of the study replied that they would be willing to participate in future studies, as opposed to 2 (13%) of the 15 who were not (P = .02). There was no correlation between patients who would be interested in participating in future studies and a perceived greater understanding of the present study or a perception of better treatment in the present study. Concern regarding the possibility of placebo therapy had no relationship to patient willingness to participate in future studies. There was also no correlation between those who reported a feeling of security and the reaction to possible future studies. Expressed patient unwillingness to participate in future studies may have included their unwillingness to suffer further heart disease and hospitalization. Patients not interested in the results of the present study were very unlikely to participate in a future trial.
The main findings of this study were that presentation of the clinical trial to the patient at the time of informed consent had a significant impact on perceived comprehension of the study, and that the most common reason given for entering the trial was the hope of receiving better medical treatment. The possibility of placebo therapy was of little or no concern to the majority of patients. Although almost all patients expressed an interest in the results of the ISIS-4 trial, only half replied that they would be willing to participate in a future study.

**ADVANTAGES AND LIMITATIONS OF MULTICENTER CLINICAL TRIALS**

Advantages of a clinical trial include access to state-of-the-art treatment and possible better patient treatment with increased attention to detail under the rigid constraints of a comprehensive case record form in addition to the standard medical annotation and source records. Enthusiasm of the health care team usually reduces time to treatment, despite the theoretical delay associated with such trial procedures as consent, randomization, and drug preparation. The time to treatment is particularly relevant in patients with acute myocardial infarction, where early treatment may limit myocardial damage and improve survival. A uniform standard of care is applied to a large number of patients worldwide.

Disadvantages of a clinical trial include choice of treatment by computer, elimination of clinical intuition by physician, and administration of placebo to a predetermined number of patients. The attention required to the study details and, in many instances, to voluminous case record forms (not so in ISIS-4) may detract from the attention the health care personnel would otherwise impart to the patient and family. The physician is encouraged to collect information (clinically relevant or not) without questioning the rationale of a study planned by a committee far away in place and time from the situation at hand, thus discouraging original thought in the physicians and trainees involved in patient treatment.

**INFORMED CONSENT AND PATIENT RECRUITMENT TO TRIALS**

There was no financial incentive to recruit patients to the ISIS-4 study, and it was assumed that patients understood that they entered the study under the rights defined in the Declaration of Helsinki. Nonetheless, almost half of the patients who returned the questionnaire believed they would receive better care if they agreed to participate in the study, and 8% agreed to participate because of fear of refusing. These data are compelling and must certainly give us pause, since it is clear that, in practice, patients actually believed that the decision to participate (or not) in the clinical trial would affect their medical care.

Participation in cardiovascular clinical trials may be influenced by numerous variables. The ISIS-4 study targeted patients suffering acute myocardial infarction, an acute medical emergency that could interfere with decisions regarding informed consent. Although recruitment to ISIS-4 was suggested after the immediate stabilization phase and after decisions regarding thrombolysis or urgent intervention, the issue was nonetheless raised during the first 24 hours after infarction (median time to randomization worldwide, 8 hours). To avoid the acute stress situation in the present study and to allow for a considered patient viewpoint, the anonymous questionnaire was mailed 1 to 3 months after the acute event, at a time when the patient could give a candid opinion regarding his or her perspective of the study.

The reasons given by the medical community for recruiting patients into clinical trials are variable. A survey of 52 oncologists identified the scientific design of the trial as the most important reason why patients were (or were not) given the option to enter clinical trials, while clinical trial nurses and family physicians gave greater weight to effects of the trial on the physician-patient relationship as a reason for participation. In a Swedish gynecologic study, 1 of 43 consenting patients was unaware that she had been in a trial, 7 were not aware of the meaning of participating in the project (including undergoing research laparoscopy), and 17 stated that they had no information about the possibility of withdrawing from the study, findings that clearly did not meet the guidelines of the Declaration of Helsinki. The data may have been less reliable, since the questionnaire was administered approximately 18 months after the trial. In patients with cancer, “total disclosure” of information at the time of consent led to better understanding but decreased patient willingness to undergo randomization and increased anxiety, although detailed informed consent before routine hernia repair did not increase patient anxiety. Consent itself could alter therapeutic outcome.

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**Table 2. Determinants of Perceived Comprehension in the ISIS-4 Trial**

<table>
<thead>
<tr>
<th>Nature of explanation</th>
<th>Perceived Comprehension of the Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Complete (n = 40)</td>
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<tr>
<td>Recollected duration of explanation</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13 10</td>
</tr>
<tr>
<td>&lt;5 min</td>
<td>27 21</td>
</tr>
<tr>
<td>≥5 min</td>
<td>28 38</td>
</tr>
<tr>
<td>Personnel giving explanation</td>
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<tr>
<td>Physician</td>
<td>10 17</td>
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<tr>
<td>Nurse</td>
<td>2 4 0</td>
</tr>
<tr>
<td>Both</td>
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<tr>
<td>Nature of explanation</td>
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</tr>
<tr>
<td>No</td>
<td>3 20 17</td>
</tr>
</tbody>
</table>

*Incomplete questionnaires account for discrepancies in numbers in the table. ISIS-4 indicates Fourth International Study of Infarct Survival; NS, not significant.*
POTENTIAL LIMITATIONS

The present study reported the findings of Israeli participants in the ISIS-4 study. The findings may have been different in other countries because of cultural and social differences. Nonetheless, the ethical issues regarding recruitment of patients and informed consent in multicenter double-blind randomized studies are similar in most parts of the world, and the present findings serve as a basis for supposition in other patients who participated in this and other trials in the circumstances of acute myocardial infarction.

The relatively low response rate to the questionnaire raises the possibility of selection bias, since it is probable that returned questionnaires were from patients with more extreme experiences (both favorable and otherwise) during the study or those interested in research. The responses were spontaneous, however, and were elicited without the pressure of repeated calls and mailings. The data probably reflect a sample of patients from a number of centers in Israel but, because of anonymity, cannot be analyzed with respect to intercenter variation.

The study was carried out in patients who entered a clinical trial in an emergency environment. The results may be different in research projects involving more stable patients with chronic diseases, who are usually outpatient patients and may consider for days and weeks rather than minutes or hours the ramifications of recruitment to a clinical trial.

IMPORTANCE OF THE STUDY

Although ethical and legal standards may seemingly be met in the conduct of a clinical trial, the present analysis showed that there is much progress to be made in the approach to patients recruited to clinical trials. Investment of time by health care practitioners to simplify consent forms and to explain treatment and research strategy to the patient is essential; it contributes to patient understanding and brings us nearer the goal of true informed consent.

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