

Influence of Gender in the Therapeutic Management of Patients with Acute Myocardial Infarction in Israel

Solomon Behar, MD, Shmuel Gottlieb, MD, Hanoch Hod, MD, Ron Narinsky, MD, Boaz Benari, MD, Eldad Rechavia, MD, Hana Pauzner, MD, Natan Rougin, MD, Oskar H. Kracoff, MD, Amos Katz, MD, Arie Roth, MD, Ehud Goldhammer, MD, Leonid Rudnik, MD, Hedy E. Faibel, MD, Chaim Lotan, MD, Chen Shapira, MD, Jamal Jafari, MD, Nahum A. Freedberg, MD, Fatchy Daka, MD, Menahem Kanetti, MD, Tedi Weiss, MD, Eddy Barasch, MD, Mark Klutstein, MD, David Blondheim, MD, Nabil Mahul, MD, Alen Gelvan, MD, and Gabriel Barbash, MD, for the Israeli Thrombolytic Survey Group*

A national study was performed in early 1992 in the 25 operating coronary care units in Israel, which enabled the assessment of whether the therapeutic management of patients with acute myocardial infarction was affected by patient gender. During a 2-month period, 1,014 consecutive patients with acute myocardial infarction were hospitalized. Thrombolytic therapy was given to 47% of men (362 of 769), and 43% of women (106 of 245) ($p = NS$). After adjustment for age, no gender differences in the administration of thrombolytic therapy were noted (odds ratio 0.95; 95% confidence interval 0.73–1.23). Coronary angiography was more frequently performed in men (22%) than in women (16%) ($p < 0.05$). However, no gender differences in the use of angioplasty or coronary bypass surgery performed during the index hospitalization were found (10% in men, and 8% in women). The main reasons for ineligibility for thrombolytic therapy were: late hospital arrival, absence of qualifying ST-T changes on admission electrocardiogram, and contraindications to thrombolytic therapy. Hospital death was significantly lower in patients receiving thrombolytic therapy (37 of 456; 8%) than in those excluded from thrombolysis (70 of 540; 13%) ($p < 0.01$). This difference was significant for men, but not for women. The 1-year postdischarge mortality was 4% in patients treated compared with 12% in those ineligible for thrombolysis ($p < 0.01$). This significant difference persisted among men and women.

(Am J Cardiol 1994;73:438–443)

From the Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, Israel. Manuscript received December 4, 1992; revised manuscript received August 13, 1993, and accepted August 16.

Address for reprints: Solomon Behar, MD, Neufeld Cardiac Research Institute, Sheba Medical Center, Tel Hashomer, 52621 Israel.

*See Appendix.

Recent studies reported differences in the use of cardiac diagnostic and therapeutic procedures between women and men hospitalized for coronary artery disease.^{1–5} Among these studies, a recent one by Maynard et al¹ reported an underutilization of thrombolytic therapy in eligible women with acute myocardial infarction (AMI). To assess whether the management of AMI was affected by patient gender, we documented the use of thrombolytic therapy and interventional procedures in men and women with AMI hospitalized in all the coronary care units in Israel in early 1992.

METHODS

A prospective survey was performed during a 2-month period (January and February 1992) in the 25 coronary care units in Israel. During the survey period, uniform guidelines for thrombolytic treatment were in use because all the coronary care units were participating in the ongoing international Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) study.⁶ According to this study protocol, patients eligible for thrombolytic treatment (1.5 million units of streptokinase, or up to 100 mg of tissue plasminogen activator) had to have typical chest pain for ≤ 6 hours, with an electrocardiogram showing ST-segment elevation ≥ 0.1 mv in ≥ 2 contiguous chest leads, in leads I and aVL, or in 2 of the 3 inferior leads (II, III and aVF).⁶ Exclusion criteria for participation in the GUSTO study were: late arrival, absence of adequate electrocardiographic changes, contraindications to thrombolytic therapy, major surgery or coronary bypass surgery within the last 6 months, history of cerebrovascular accident, and recent cardiopulmonary resuscitation. Patients ineligible for the GUSTO study could receive thrombolytic treatment at the discretion of the treating staff. Patients who received thrombolytic treatment not according to the GUSTO protocol were included in the analysis. The diagnosis of AMI was based on typical chest pain lasting ≥ 30 minutes, unequivocal electrocardiographic (new Q/QS or ST-T, or both) changes and an increase in serum levels of cardiac enzymes (creatinine kinase-MB+, glutamic oxaloacetic transaminase and lactate dehydrogenase). Data recorded during hospitalization included age, gender, history of AMI, and infarct site. The reasons for ineligibility to GUSTO, and the types of diagnostic or therapeutic pro-

| | Thrombolytic Therapy | | p Value |
|----------------------------|----------------------|------------------|---------|
| | Yes (n = 468) (%)* | No (n = 546) (%) | |
| Men | 362 (77) | 407 (75) | NS |
| Mean age (years) | 60.5 ± 12.0 | 64.7 ± 13.0 | <0.0001 |
| Previous infarction | 83 (18) | 181 (33) | <0.001 |
| Myocardial infarction site | | | <0.001 |
| Anterolateral | 249 (53) | 231 (42) | |
| Inferoposterior | 213 (46) | 235 (43) | |
| Coronary angiography | 114 (24) | 98 (18) | 0.01 |
| Coronary angioplasty | 38 (8) | 34 (6) | NS |
| Bypass surgery | 16 (3) | 9 (2) | NS |

*384 patients were included in GUSTO study, and 84 were given streptokinase not per GUSTO protocol (see Methods).

| | Men (n = 769) (%) | Women (n = 245) (%) | p Value |
|---------------------|-------------------|---------------------|---------|
| | Age | | |
| ≤ 65 years | 479 (62) | 80 (33) | <0.001 |
| > 65 years | 290 (38) | 165 (67) | <0.001 |
| Mean (years) | 61.0 ± 12.8 | 68.2 ± 10.7 | <0.0001 |
| Previous infarction | 214 (28) | 50 (20) | <0.01 |
| Non-Q wave | 54 (7) | 11 (4) | NS |
| Q-wave site | | | |
| Anterolateral | 368 (48) | 112 (46) | NS |
| Inferoposterior | 334 (43) | 114 (47) | NS |
| Other | 10 (1) | 6 (2) | NS |

cedures performed during the index hospitalization were recorded also. Hospital and 1-year postdischarge mortality were assessed for all patients participating in the survey by matching the ID number of patients with the Israeli National Population Register.

Statistical analysis: Chi-square and *t* tests were used to determine the significance of the differences between men and women regarding proportions and means, respectively. All tests were 2-tailed. Logistic regression analysis was performed, adjusting for potential variables (age, gender, history of AMI, and location of the index AMI) that may influence the use of thrombolytic treatment and invasive procedures during AMI.⁷

RESULTS

During the survey, 1,014 patients (769 men and 245 women) were hospitalized for AMI. Of these patients, 384 (38%) were enrolled in the GUSTO study, and 84 (8%) were treated with 1,500,000 units of streptokinase, although they were considered ineligible by the GUSTO protocol (see Methods). Thus, in all, the number of patients in this survey with AMI treated with a thrombolytic agent was 468 (46%).

The baseline characteristics and use of invasive coronary procedures in patients with and without thrombolytic treatment are presented in Table I. Patients treated with thrombolytic therapy were 4 years younger, and more often had a first and anterior wall AMI as compared with those ineligible for thrombolytic therapy. Coronary angiography was performed more frequently in patients who received thrombolytic therapy.

Baseline characteristics and wall site of AMI of patients according to gender are listed in Table II. Women

| | Men | Women |
|------------------------------|---------------|---------------|
| | (n = 769) (%) | (n = 245) (%) |
| Age | | |
| ≤ 65 years | 250/479 (52) | 40/80 (50) |
| > 65 years | 112/290 (39) | 66/165 (40) |
| First myocardial infarction | 291/537 (54) | 92/188 (49) |
| Previous infarction | 69/214 (32) | 14/50 (28) |
| Q-wave myocardial infarction | | |
| Anterolateral | 195/368 (53) | 54/112 (48) |
| Inferoposterior | 163/334 (49) | 50/114 (44) |
| Total | 362/769 (47) | 106/245 (43) |

were, on the average, 7 years older and had a lower incidence of previous AMI as compared with men. No other difference was observed between the 2 genders.

Forty-seven percent of men versus 43% of women (*p* = NS) received thrombolytic treatment (Table III). The frequency of thrombolytic therapy was equal between both genders in subgroup analysis by: age group (< and >65 years), AMI number (first vs recurrent), and wall site of index AMI (anterior vs inferior or posterior) (Table III). Moreover, the use of thrombolytic treatment was similar in both genders with the GUSTO protocol (men: 39%; and women: 32%; *p* = NS) or in patients ineligible for GUSTO (men: 13%; and women: 15%; *p* = NS). The frequency of coronary angiography was lower in women only in the older age group (Table IV). Coronary angioplasty or bypass surgery were performed with the same frequency in both genders (Table IV).

To examine the independence of the relation of gender to each therapy provided, a multivariate regression analysis was performed after controlling for parameters obtained during hospitalization (see Methods). After adjustments for age, history of previous infarction and location of the index AMI, no gender difference in the use of each therapy examined was observed (Table V).

The reasons for exclusion of patients from thrombolytic therapy by gender are shown in Figure 1. Late arrival to the coronary care unit was the major reason for not providing thrombolytic therapy to women.

In-hospital mortality was lower in patients treated with thrombolytic therapy than in those ineligible for this treatment (Table VI).

The 1-year postdischarge mortality was threefold higher in patients ineligible for thrombolytic treatment than in those treated with thrombolysis (Table VII). This difference persisted among men and women, and in subgroup analysis by age and number of previous AMIs (Table VII). Figures 2 and 3 represent the Kaplan-Meier 1-year survival curves for men and women with and without thrombolytic therapy.

DISCUSSION

Frequency of use of thrombolytic therapy and interventional procedures: The results of this national survey attest against gender selection bias for thrombolytic therapy. The data differ from earlier reports by

| | Men (n = 769) (%) | | | Women (n = 245) (%) | | |
|----------------------|-------------------|------------|-------|---------------------|------------|------|
| | ≤ 65 Years | > 65 Years | All | ≤ 65 Years | > 65 Years | All |
| | (n = 479) | (n = 290) | | (n = 80) | (n = 165) | |
| Coronary angiography | 124 (26) | 49 (17) | (22)* | 22 (27) | 17 (10) | (16) |
| Coronary angioplasty | 43 (9) | 15 (5) | (8) | 9 (11) | 5 (3) | (6) |
| Bypass surgery | 12 (3) | 8 (3) | (3) | 1 (1) | 4 (2) | (2) |

*p < 0.05 comparing coronary angiography use between men and women.

| Therapy or Intervention | Men (n = 769) | Women (n = 245) | Odds Ratio | 95% CI |
|--------------------------|---------------|-----------------|------------|-----------|
| Thrombolytic therapy (%) | 47 | 43 | 0.95 | 0.73-1.23 |
| Coronary angiography (%) | 22* | 16 | 0.87 | 0.58-1.30 |
| Coronary angioplasty (%) | 8 | 8 | 1.02 | 0.55-1.88 |
| Coronary bypass (%) | 3 | 2 | 0.76 | 0.28-2.08 |

*p < 0.02 by univariate analysis.
CI = confidence interval.

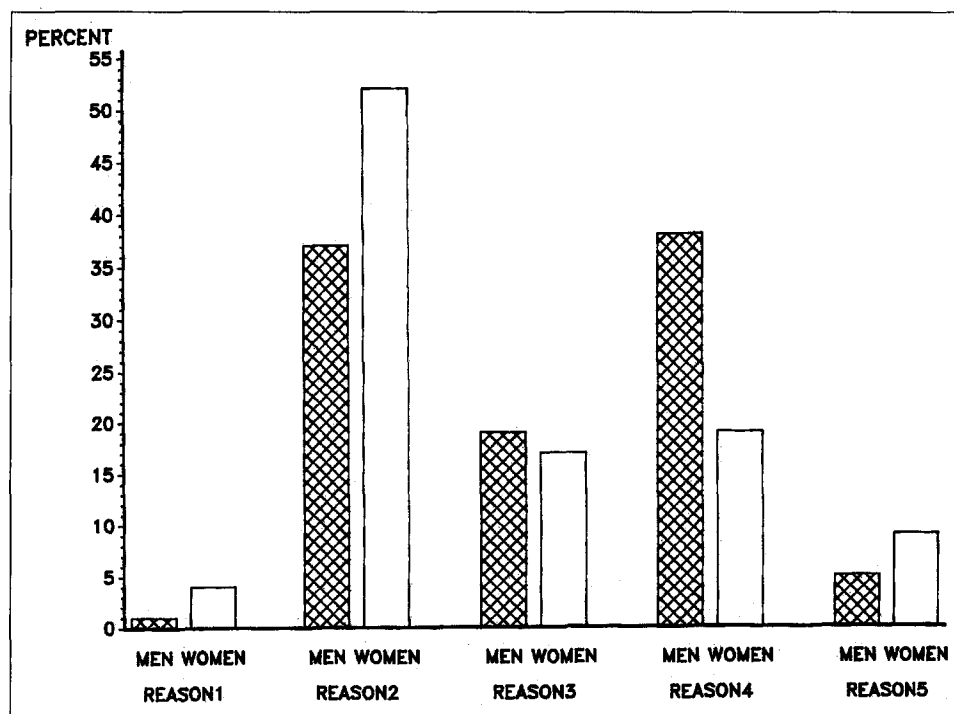


FIGURE 1. Reasons for ineligibility for GUSTO by gender: (1) old age; (2) late arrival; (3) contraindications to thrombolytic therapy; (4) unqualifying entry electrocardiogram; and (5) other.

Maynard et al¹ who found that 17% of women compared with 26% of men with AMI received thrombolytic treatment. An imbalance in the distribution of men to women was observed also in the SAVE study in which of 2,231 patients recruited from 112 coronary care units from the United States and Canada, 24% of women compared with 35% of men ($p = 0.0001$) received thrombolytic therapy.⁸

The similarity in rates of thrombolytic treatment among men and women in the present survey may have been due to patient recruitment through a thrombolytic trial protocol; thus, potential selection bias related to physician judgement may have been attenuated. However, the absence of gender bias in the frequency of thrombolytic treatment among patients who were ineligible for the GUSTO study suggests that the equal use of thrombolytic therapy in both genders was not related to GUSTO.

As reported by other investigators,^{3,4} coronary angiography was more frequently used in men than in women in this study. However, the difference was pres-

ent only in elderly patients (Table IV) who included a higher proportion of women. In contrast, revascularization procedures (coronary angioplasty and bypass

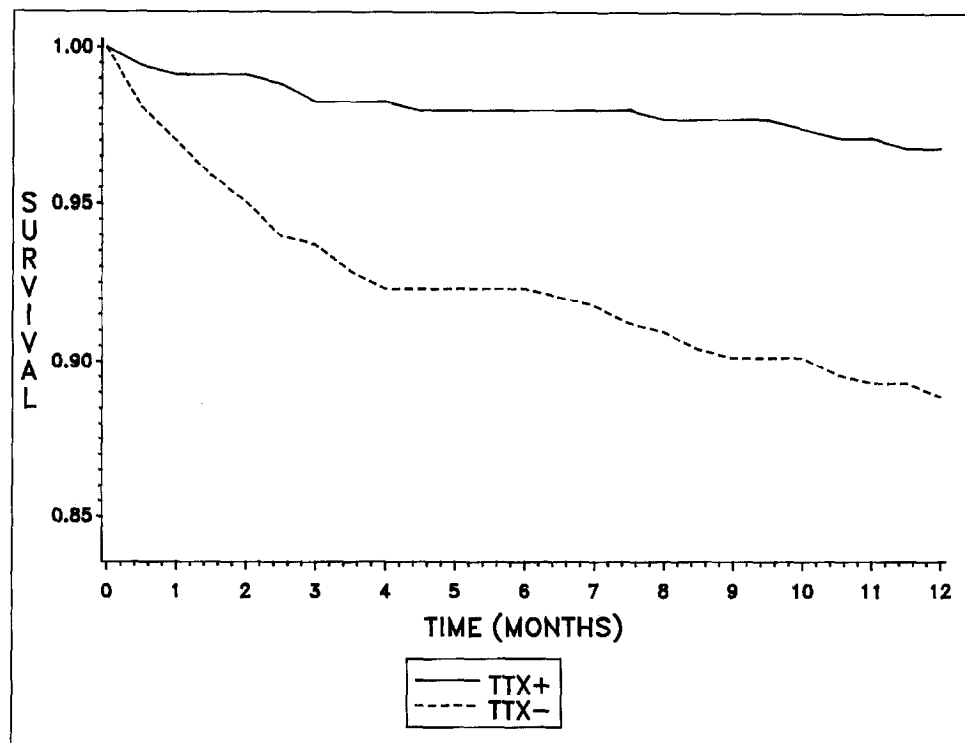
TABLE VI In-Hospital Death

| | Thrombolytic Therapy (%) | | p Value |
|---------------------------------------|--------------------------|--------------|---------|
| | Yes (n = 468) | No (n = 546) | |
| Men | 22/362 (6) | 43/407 (11) | <0.03 |
| Women | 15/106 (14) | 27/139 (19) | NS |
| Age | | | |
| ≤ 65 years | 12/290 (4) | 20/269 (7) | NS |
| > 65 years | 25/178 (14) | 50/277 (18) | NS |
| First myocardial infarction | 26/383 (7) | 37/342 (11) | <0.05 |
| Recurrent myocardial infarction | 11/83 (13) | 30/181 (17) | NS |
| Anterior myocardial infarction | 24/237 (10) | 35/195 (18) | <0.02 |
| Inferoposterior myocardial infarction | 10/213 (5) | 22/235 (9) | <0.06 |
| Total | 37/468 (8) | 70/546 (13) | <0.01 |

TABLE VII One-Year Postdischarge Mortality

| | Thrombolytic Therapy | | p Value |
|---------------------------------|----------------------|------------------|---------|
| | Yes (n = 431) (%) | No (n = 476) (%) | |
| Men | 11/340 (3) | 42/364 (12) | <0.001 |
| Women | 5/91 (5) | 17/112 (15) | <0.03 |
| Age | | | |
| ≤ 65 years | 8/278 (3) | 22/249 (9) | <0.01 |
| > 65 years | 8/153 (5) | 37/227 (16) | <0.01 |
| First myocardial infarction | 8/357 (2) | 30/305 (10) | <0.001 |
| Recurrent myocardial infarction | 7/72 (10) | 25/151 (17) | NS |
| Total | 16 (4) | 59 (12) | <0.001 |

FIGURE 2. Survival curves of men treated (TTX+) and not treated (TTX-) with thrombolytic therapy.



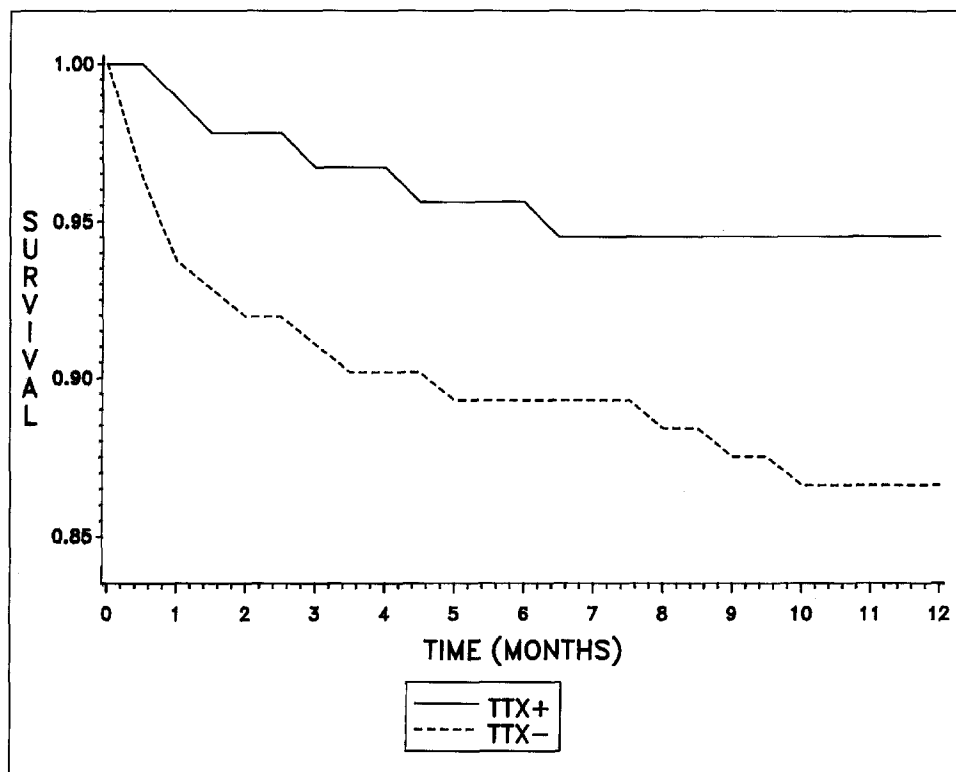


FIGURE 3. Survival curves of women treated (TTX+) and not treated (TTX-) with thrombolytic therapy.

surgery) were performed equally in men and women. One recent study also reported equal use of coronary angiography and angioplasty in the early phase of AMI in men and women, as well as equal rates of coronary bypass surgery for severely symptomatic patients after AMI.⁵ It is not possible to conclude from earlier reports whether cardiac catheterization and coronary bypass surgery were underused in women or overused in men.⁴ It is not clear from the data if these rates reflect appropriate clinical practice or if the outcome in women with coronary artery disease is compromised by this difference.³

The results suggest that in men and women presenting with a similar cardiac diagnosis (evolving AMI), thrombolytic therapy, and other diagnostic and therapeutic procedures are used equally in both genders. The similar rates of invasive coronary procedures in both genders may result from the adoption of the conservative ("watchful waiting") strategy that advocates use of these procedures only in patients with clear-cut clinical indications and minimizes the decision power of the treating physician.

Reasons for exclusion of patients from thrombolysis: In accordance with our previous surveys, the main reasons for excluding patients from thrombolytic treatment were late arrival to the hospital, and absence of qualifying electrocardiographic changes for both men and women.^{9,10} Late arrival to the hospital was the leading cause of exclusion of women in the present study. Contraindications to thrombolytic treatment were present equally in both genders.

Early mortality: As expected, hospital mortality was significantly lower in patients receiving thrombolytic treatment. However, the difference did not achieve statistical significance in women. These results may have

been hampered by the relatively small number of women (n = 245). A significant reduction of in-hospital mortality was observed in patients treated by thrombolytic therapy with a first episode of AMI, as well as in both AMI locations (anterior and inferior or posterior).

Late mortality: Subsequent 1-year mortality was high (12%) in patients excluded from thrombolytic treatment, particularly in women (15%), the elderly (aged >65 years; 16%) and those with recurrent AMI (17%); these high mortality statistics contrast with the relatively low 1-year postdischarge mortality in their counterparts treated with thrombolytic therapy (3, 5 and 10%, respectively) (Table VII). Although patients who received thrombolytic treatment were younger and included more cases with a first AMI, the beneficial effect of reperfusion therapy in all subgroups of patients appears to be more than probable.

Acknowledgment: We are indebted to all nurses and physicians working in the coronary care units in Israel, Yemima Nahum and Dalia Ben-David for collection of data. We are most grateful to Mark Goldberg for programming the data base, Valentina Boyko for statistical analysis, Lynn Goodman for technical assistance in preparing the manuscript, and Lori Mandelzweig for editorial assistance. We thank Monty Zion, MD, and Elieser Kaplinsky, MD, for reviewing the manuscript.

APPENDIX

Participating centers and directors of the cardiac departments: Assaf Harofeh Hospital, Zerifin: Zwi Schlesinger, MD; Barzilai Medical Center, Ashkelon: Leonardo Reisin, MD; Beilinson Medical Center, Petach Tikvah: Samuel Sclarovsky, MD; Bikur

Holim, Jerusalem: principal investigator: Shlomo Stern, MD; Bnei Zion Medical Center, Haifa: Edward Abinader, MD; Carmel Hospital, Haifa: principal investigator: Bazel Luis, MD; Carmel Hospital and Medical "Lin" Haifa, Haifa: Abraham Palant, MD; Central Emek Hospital, Afula: Tiberiu Rosenfeld, MD; Hadassah, Ein Kerem, Jerusalem: Mervyn Gotesman, MD; Hadassah, Har HaZofim, Jerusalem: Tedi Weiss, MD; Hasharon Hospital, Petach Tikvah: Izhar Zahavi, MD; Hillel Yaffe Hospital, Hadera: Benyamin Pelled, MD, MSc; Ichilov Hospital, Sourasky Medical Center, Tel Aviv: Shlomo Laniado, MD; Josephtal Medical Center, Eilat: Alen Gelvan, MD; Kaplan Hospital, Rehovot: Avraham Caspi, MD; Laniado Hospital, Netanya: Eddy Barasch, MD; Meir Hospital, Kfar Saba: Daniel David, MD; Poriah Hospital, Tiberius: Leonid Rudnik, MD; Rambam Medical Center, Haifa: Walter Markiewicz, MD; Rivka Ziv Medical Center, Tsfat: Alon Marmour, MD; Shaare Zedek Medical Center, Jerusalem: Daniel Tzivoni, MD; Sheba Medical Center, Tel Hashomer: Elieser Kaplinsky, MD; Soroko Medical Center, Beer Sheva: Natalio Cristal, MD; Western Galilee Hospital, Naharia: Natan Rougin, MD; and Wolfson Medical Center, Holon: Yehezkiel Kishon, MD.

1. Maynard C, Althouse R, Cerqueira M, Olsufka M, Kennedy JW. Underutilization of thrombolytic therapy in eligible women with acute myocardial infarction.

Am J Cardiol 1991;68:529-530.

2. Tobin JN, Wasshethel-Smoller S, Wexler JP, Steingart RM, Budner N, Lense L, Wachspress J. Sex bias in considering coronary bypass surgery. *Ann Intern Med* 1987;107:19-25.

3. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary heart disease. *N Engl J Med* 1991;325:221-225.

4. Steingart RM, Packer M, Hamm P, Coglianesi ME, Gersh B, Geltman EM, Solano J, Katz S, Moye L, Basta LL, Lewis SJ, Gottlieb SS, Berstein V, McEwan P, Jacobson K, Brown EJ, Kukin ML, Kantrowitz NE, Pfeffer MA for the Survival and Ventricular Enlargement Investigators. Sex differences in the management of coronary artery disease. *N Engl J Med* 1991;325:226-230.

5. Krumholz HM, Douglas PS, Lauer MS, Pasternal RC. Selection of patients for coronary angiography and coronary revascularization early after myocardial infarction: is there evidence for a gender bias? *Ann Intern Med* 1992;116:785-790.

6. Topol EJ, Armstrong P, Van de Werf F, Kleiman N, Lee K, Morris D, Simoons M, Barbash G, White H, Califf RM, on behalf of the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Steering Committee. Confronting the issues of patient safety and investigator conflict of interest in an international clinical trial of myocardial reperfusion. *J Am Coll Cardiol* 1992;19:1123-1128.

7. Logistic Procedure. SAS/STAT User's Guide, Version 6, 4th ed. Cary, North Carolina: SAS Institute Inc., 1989;1:1077-1126.

8. Pfeffer MA, Moye LA, Braunwald E, Basta L, Brown EJ Jr, Cuddy TE, Dagenais GR, Flaker GC, Gersh BJ, Goldman S, Lamas GA, Packer M, Rovleau JL, Rutherford J, Steingart RM, Wertheimer JH, for the SAVE Investigators. Selection bias in the use of thrombolytic therapy in acute myocardial infarction. *JAMA* 1991;266:528-532.

9. Behar S, Hod H, Barbash G, Kaplinsky E. Incidence of and reasons for excluding patients with acute myocardial infarction from thrombolytic therapy. *Isr J Med Sci* 1991;27:121-123.

10. Behar S, Abinader E, Caspi A, David D, Flich M, Friedman Y, Hod H, Kaplinsky E, Kishon Y, Kristal N, Laniado S, Markiewicz W, Marmour A, Palant A, Pelled B, Reisin L, Rosenfeld T, Roguin N, Sherf L, Rabinowitz B, Schlesinger Z, Sclarovsky S, Zahavi I, Zion M, Goldbourt U, for the SPRINT Study Group. Frequency of use of thrombolytic therapy in acute myocardial infarction in Israel. *Am J Cardiol* 1991;68:1291-1294.