Treatment Program for Erectile Dysfunction in Patients With Cardiovascular Diseases

Solomon Israilov, MD, Jack Baniel, MD, Joseph Shmueli, MD, Eva Niv, MD, Dov Engelstein, MD, Ephraim Segenreich, MD, and Pinhas M. Livne, MD

The present study assesses the effectiveness of our progressive treatment program for erectile dysfunction in patients with cardiovascular diseases. The study sample included 453 patients aged 36 to 91 years. Therapy in all patients was begun with sildenafil citrate 25 to 100 mg. Those with contraindications, drug adverse effects, or a negative response (erection insufficient for vaginal penetration) were given intracavernous injections of a cocktail of vasoactive drugs (dimix, trimix, or quadmix), followed by the addition of sildenafil citrate to the trimix in case of failure, and then a penile prosthesis. Patients were followed for 2 years; in cases of treatment ineffectiveness during follow-up, drug dosages were increased or a penile prosthesis was suggested. Sildenafil citrate was offered to 417 patients of whom 205 (49.2%) responded positively. The remaining 248 patients received intracavernous injections: 135 (54.4%) had a positive response to the dimix, 85 (75.2%) to the trimix, and 16 (57.1%) to the quadmix. Four of the other 12 patients (0.9%) responded to sildenafil citrate + trimix, and 2 (0.4%) agreed to a penile prosthesis. At the 2-year follow-up of 447 patients, 131 (29.3%) were successfully treated with sildenafil citrate, 92 (20.6%) with dimix, 122 (27.3%) with trimix, 12 (2.7%) with quadmix, and 2 (0.4%) with sildenafil citrate + trimix; 5 patients (1.1%) had a penile implant. Forty-eight patients (10.7%) achieved spontaneous erection, of whom 46 were taking aspirin. Twenty-six patients (5.8%) stopped treatment because of health and family reasons and 9 (2%) had a negative response. Our progressive treatment program for erectile dysfunction has a high success rate in patients with cardiovascular disease: Overall, 98.7% achieved an erection sufficient for vaginal penetration immediately after the trial and 92.2% on follow-up; 10.7% achieved spontaneous erections. ©2004 by Excerpta Medica, Inc.

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analysis, and medical, social, and psychiatric history of the patient and his partner, physical examination, nocturnal penile tumescence test with RigiScan (Dacomed, Minneapolis, Minnesota), penile color Doppler ultrasound, and laboratory findings (glucose loading, levels of cholesterol, triglycerides, creatinine, creatine phosphokinase, prolactin, and total testosterone).

**Procedure:** All patients without contraindications were offered sildenafil citrate, 1 tablet 1 hour before coitus or sexual activity, 2 to 3 hours after a meal. The starting dose was 25 mg, which was increased to 50 and 100 mg at intervals of 2 to 4 days, depending on response, age, and general state of health. A positive response in the present study was defined as an erection sufficient for vaginal penetration. Patients with contraindications, adverse effects of the drug, or a negative response were given intracavernous injections of a cocktail of vasoactive drugs. Patients were started on a combination of papaverine 8 to 25 mg and phentolamine 0.05 to 2.0 mg (dimix) depending on age and state of health. Three trials with dimix were conducted at intervals of 3 to 6 days. Patients who responded were instructed to self-inject the mixture at home 5 to 15 minutes before coitus. Treatment that was unsuccessful was switched to trimix: papaverine 15 to 25 mg + phentolamine 1.5 to 2.0 mg + prostaglandin E1 10 to 25 μg. In patients who complained of pain during erection, the prostaglandin dose was decreased and the doses of the other drugs increased. Patients who failed to respond to trimix were switched to quadmix: papaverine 18 to 25 mg + phentolamine 1.5 to 2.0 mg + prostaglandin E1 12 to 25 μg + atropine sulfate 0.03 to 0.08 mg. Two trial sessions were conducted, with dosage increases within the prescribed range, as necessary. If quadmix was ineffective, patients were given sildenafil citrate 50 to 100 mg, followed after 30 to 45 minutes by an intracavernous injection of trimix: papaverine 16 to 20 mg + phentolamine 1.2 to 1.6 mg + prostaglandin E1 15 to 25 μg. Patients who still failed to respond were offered a penile prosthesis.

**Follow-up:** Patients were followed for 2 years. During this time they remained under the care of their cardiologist or family physician for management of the cardiovascular disease. Every 2 to 4 months, we took a medical, social, and psychosocial history with the patients alone and with their partners. Nonresponders who started with sildenafil were switched to a higher dose (100 mg) or to intracavernous injections (dimix to trimix to quadmix) alone or, in case of failure, sildenafil plus intracavernous injection with trimen and penile implant. Patients receiving intracavernous drugs underwent a physical examination at each visit to rule out fibrotic nodules or areas of scarring. Penile color Doppler ultrasound and nocturnal penile tumescence testing were performed annually.

**Statistical analysis:** Results were analyzed with standard statistical tests, including descriptive statistics, Student’s t test, and linear regression analysis. A p value <0.05 was considered statistically significant.

### RESULTS

During retrospective analysis, we found that all patients reported normal erectile function before appearance of cardiovascular diseases; 213 (47%) attributed the ED to medication for the cardiovascular diseases, 97 (21.4%) to surgery they underwent for cardiovascular diseases, and 143 (31.6%) to a combination of medication, surgery, and age. In 94 patients (44.1%) in the first group, sexual function improved for 2 to 4 months after a change in medication and then deteriorated again.

**Severity of ED:** According to the IIEF scores before treatment, ED was severe (score 1 to 10) in 189 patients (41.7%), moderate (score 10 to 16) in 171 (37.7%), mild to moderate (score 17 to 20) in 68 (15%), and mild (score 21 to 25) in 25 (5.5%). The duration of ED was 6 months to 18 years (mean ± SD 2.5 ± 1.2).

**Phase I—sildenafil citrate:** Thirty-six patients (7.9%) had contraindications for sildenafil, namely long-term nitrate therapy in 14 (3.1%), recent (1 to 1.5 months) bypass surgery in 5 (1.1%), recent (1 to 2 months) myocardial infarct in 4 (0.9%), unstable angina pectoris in 6 (1.3%), unstable hypertension in 5 (1.1%), and valve replacement in 2 (0.4%). Of the remaining 417 patients, 205 (49.2%) had a positive response to sildenafil and 73 (17.5%) had adverse effects. The doses of sildenafil are listed in Table 1. In the responders, the erection occurred 20 minutes to 1 hour (mean ± SD 45.4 ± 4.5 minutes) after drug ingestion and lasted for 15 to 40 minutes (mean ± SD 25.4 ± 4.8).

Seventy-three patients had various adverse effects: facial flushing in 25 (6%), headache in 20 (4.8%), dizziness in 7 (1.7%), tachycardia in 9 (2.2%), abnormal vision in 5 (1.2%), dyspepsia in 3 (0.7%), and chest pain in 4 (1%).

**Phase II—dimix:** Patients with contraindications for sildenafil citrate and patients who were unsuccessful with sildenafil citrate treatment (including those with adverse effects) (n = 248) received the first injection of dimix (papaverine 8 to 12 mg + phentolamine 0.05 to 0.6 mg). Forty-seven (18.9%) responded to the first injection, 79 of the remaining 201 (39.3%) to the second injection, and 9 of the remaining 122 (7.4%) to the third injection. Duration of the response to the first injection was 32 to 240 minutes, to the second injec-

### TABLE 1 Positive Response and Adverse Effects by Dose in 417 Patients Receiving Sildenafil Citrate

<table>
<thead>
<tr>
<th>Sildenafil Citrate Dose (mg)</th>
<th>No. of Patients</th>
<th>Positive Response (n = 205)</th>
<th>Negative Response (n = 139)</th>
<th>Adverse Effects (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>417</td>
<td>15 (3.6%)</td>
<td>398 (95.4%)</td>
<td>4 (1.0%)</td>
</tr>
<tr>
<td>50</td>
<td>398</td>
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<td>12 (3.0%)</td>
</tr>
<tr>
<td>100</td>
<td>325</td>
<td>129 (36.7%)</td>
<td>135 (42.8%)</td>
<td>57 (17.5%)</td>
</tr>
<tr>
<td>Total</td>
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<td><strong>33.3%</strong></td>
<td><strong>73 (17.5%)</strong></td>
</tr>
</tbody>
</table>

**Adverse Effects:**

- **Phosphodiesterase-5 inhibitors:**
  - **Sildenafil citrate:**
    - *Side effects:
      - **Common (≥10%):** Headache, flushing, dyspepsia, back pain, myalgia, nasal congestion, decreased libido, nasal dryness, diaphoresis, constipation, dyspepsia, vasodilation, chest pain, and dizziness.
      - **Rare (≥0.1%):** Tachycardia, hypotension, syncope, and priapism.
  - **Dosage:**
    - Classic: 50 mg (regimen: 1 tablet 1 hour before coitus or sexual activity, 2 to 3 hours after a meal).
    - Extended: 100 mg (for patients with low blood pressure or those who have had previous reactions to 50 mg).
  - **Contraindications:**
    - Hypotension (mean arterial pressure <90 mmHg), severe vasodilatation (mean arterial pressure <50 mmHg), priapism, and allergic reactions to dimix to trimix to quadmix.

### References

1. **Phase I:**
   - Dose:
     - Classic: 50 mg (regimen: 1 tablet 1 hour before coitus or sexual activity, 2 to 3 hours after a meal).
     - Extended: 100 mg (for patients with low blood pressure or those who have had previous reactions to 50 mg).
   - Contraindications:
     - Hypotension (mean arterial pressure <90 mmHg), severe vasodilatation (mean arterial pressure <50 mmHg), and allergic reactions to dimix to trimix to quadmix.

2. **Phase II:**
   - Dose:
     - Classic: 50 mg (regimen: 1 tablet 1 hour before coitus or sexual activity, 2 to 3 hours after a meal).
     - Extended: 100 mg (for patients with low blood pressure or those who have had previous reactions to 50 mg).
   - Contraindications:
     - Hypotension (mean arterial pressure <90 mmHg), severe vasodilatation (mean arterial pressure <50 mmHg), and allergic reactions to dimix to trimix to quadmix.

3. **Dose:**
   - Classic: 50 mg (regimen: 1 tablet 1 hour before coitus or sexual activity, 2 to 3 hours after a meal).
   - Extended: 100 mg (for patients with low blood pressure or those who have had previous reactions to 50 mg).
   - Contraindications:
     - Hypotension (mean arterial pressure <90 mmHg), severe vasodilatation (mean arterial pressure <50 mmHg), and allergic reactions to dimix to trimix to quadmix.

### Table 1

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<th>Sildenafil Citrate Dose (mg)</th>
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<th>Negative Response (n = 139)</th>
<th>Adverse Effects (n = 73)</th>
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<td><strong>33.3%</strong></td>
<td><strong>73 (17.5%)</strong></td>
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</table>
tion 65 to 180 minutes, to the third 35 to 54 minutes (mean 81.4 ± 4.5, 71.4 ± 3.5, 38.6 ± 1.4, respectively). In all, 135 patients (54.4%) achieved a positive response in phase.

**Phase III**—trimix: One hundred thirteen patients received the first trimix injection (papaverine 15 mg + phentolamine 1.5 mg + prostaglandin E1 10 μg), and 72 had a positive response (63.7%); duration of the response was 40 to 180 minutes (mean 63.3 ± 3.6). However, 62 responders (54.9%) complained of pain during erection, so the dosage of prostaglandin E1 was reduced concomitant with an increase in papaverine and phentolamine. Of the 41 patients who needed a second injection (papaverine 25 mg + phentolamine 2.0 mg + prostaglandin E1 25 μg), 13 (31.7%) had a positive response; the duration of the response was 36 to 84 minutes (mean 53.3 ± 2.1). In total, 85 patients (75.2%) achieved a positive response in phase III.

**Phase IV**—quadmix: Of the 28 patients who received the quadmix injection (papaverine 18 mg + phentolamine 1.5 mg + prostaglandin E1 12 μg + atropine sulfate 0.03 mg), 12 (42.9%) had a positive response to the first injection. Duration of the response was 46 to 86 minutes (mean 54.4 ± 2.1); 4 patients (25%) responded to the second injection (papaverine 25 mg + phentolamine 2.0 mg + prostaglandin E1 25 μg + atropine sulfate 0.08 mg). The duration of the response was 32 to 71 minutes (mean 42.2 ± 2.1). The total number of positive responses in this phase was 16 patients (57.1%).

The analysis of positive response in phases I to IV depended on type of cardiovascular disease (Table 2).

**Phase V**—sildenafil citrate + intracavernous injections: Of the remaining 12 patients, 2 (16.7%) had a positive response to sildenafil 50 mg, followed 30 to 45 minutes later by an intracavernous injection of trimix-papaverine 16 mg + phentolamine 1.2 mg + prostaglandin E1 15 μg. Two patients (20% of the remaining patients) had a positive response to sildenafil citrate 100 mg, followed by trimix-papaverine 20 mg + phentolamine 1.6 mg + prostaglandin E1 25 μg.

**Phase VI**—penile implant: Two of 8 patients who had no success agreed to surgical intervention with a penile implant. Both the intra- and postoperative periods were free of complications. Patients performed successful coitus after 6 to 7 weeks.

**Follow-up:** The 447 patients with a positive response to the progressive program were observed for 2 years (Table 3). Sildenafil citrate was found to be successful in 29.3%, dimix in 20.6%, trimix in 27.3%, quadmix in 2.7%, sildenafil + injection in 0.4%, and penile prosthesis in 1.1%. Comparison of the IIEF scores at baseline with those at the end of follow-up (Table 4) indicated a significant reduction in the rate of severe ED, from 48.2 ± 0.4% in patients before treatment to 14.4 ± 0.2% after treatment (p < 0.001).

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**Table 2: Positive Response to Phases I to IV in Relation to Type of Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Cardiovascular Diseases</th>
<th>No. of Patients</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Phase IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Sildenafil Citrate (n = 417)</td>
<td>Dimix (n = 248)</td>
<td>Trimix (n = 113)</td>
<td>Quadmix (n = 28)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>113</td>
<td>67 (59.3%)</td>
<td>24 (21.2%)</td>
<td>22 (19.5%)</td>
<td>–</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>31</td>
<td>–</td>
<td>24 (77.4%)</td>
<td>7 (22.6%)</td>
<td>–</td>
</tr>
<tr>
<td>Arrhythmia and hypertension</td>
<td>44</td>
<td>–</td>
<td>26 (63.6%)</td>
<td>16 (36.4%)</td>
<td>–</td>
</tr>
<tr>
<td>Valve disease and hypertension*</td>
<td>15</td>
<td>–</td>
<td>6 (40%)</td>
<td>6 (40%)</td>
<td>–</td>
</tr>
<tr>
<td>Hypertension</td>
<td>126</td>
<td>76 (60.3%)</td>
<td>30 (23.8%)</td>
<td>20 (15.9%)</td>
<td>–</td>
</tr>
<tr>
<td>Coronary artery disease and hypertension†</td>
<td>119</td>
<td>61 (51.3%)</td>
<td>25 (21%)</td>
<td>14 (11.8%)</td>
<td>10 (8.4%)</td>
</tr>
<tr>
<td>After cerebrovascular accident and hypertension</td>
<td>5</td>
<td>1 (20%)</td>
<td>4 (80%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>453</td>
<td>205 (45.2%)</td>
<td>135 (29.8%)</td>
<td>85 (18.8%)</td>
<td>16 (3.5%)</td>
</tr>
</tbody>
</table>

*No success in 3 patients.
†No success in 9 patients.

**Table 3: Findings at Follow-up**

<table>
<thead>
<tr>
<th>Positive Response After Progressive Treatment Program</th>
<th>Positive Response for Each Phase</th>
<th>Stopped Treatment</th>
<th>Positive Response After 2 yrs of Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil citrate (n = 205)</td>
<td>131 (63.9%)</td>
<td>2 (0.4%)</td>
<td>10 (2.2%)</td>
</tr>
<tr>
<td>Dimix (n = 135)</td>
<td>67 (49.6%)</td>
<td>2 (0.4%)</td>
<td>5 (1.1%)</td>
</tr>
<tr>
<td>Trimix (n = 85)</td>
<td>63 (74.1%)</td>
<td>4 (0.8%)</td>
<td>8 (1.8%)</td>
</tr>
<tr>
<td>Quadmix (n = 16)</td>
<td>7 (43.7%)</td>
<td>1 (0.2%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Sildenafil citrate + intracavernous injection (n = 4)</td>
<td>2 (50.0%)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Penile prosthesis (n = 2)</td>
<td>2 (100%)</td>
<td>–</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td>Total (n = 447)</td>
<td>272 (60.8%)</td>
<td>9 (2.0%)</td>
<td>26 (5.8%)</td>
</tr>
</tbody>
</table>

*Went from 1 phase to another due to a negative response.
†Not switched to other phases.
§Switched from 1 phase to another.
We compared positive response with the severity of ED. Of 189 patients with severe ED, a positive response was seen in 17 with dimix (9%), in 122 with trimix (64.6%), in 12 with quadmix (6.3%), and in 2 with sildenafil citrate + trimix (1.1%); a penile implant was deployed in 5 patients (2.6%). Of 171 with moderate ED, a positive response was seen in 65 patients with sildenafil citrate (38%), in 90 with dimix (52.6%), in 13 with trimix (7.6%), and in 3 with quadmix (1.8%). Of 68 patients with mild-to-moderate ED, 8 (11.8%) had a positive response with dimix, and sildenafil citrate was effective in the remaining patients. Sildenafil citrate was effective in all 25 patients with mild ED. A negative response was seen in 15 patients (3.3%) with severe ED.

In all, 41 of 453 patients (9%) discontinued treatment: 26 (5.7%) because of a family situation and a poor state of health, 15 (3.3%) because of no success. An analysis of the reasons for discontinuing treatment revealed that 26 patients were elderly (aged 74 to 91) and 12 of them (46.2%) were divorced. 9 (34.6%) were widows, and 5 (19.2%) were married to women who had illnesses. Analysis of the reasons for the ineffectiveness of the progressive treatment in these 15 patients (3.3%) revealed that 3 of them were receiving 4 to 8 different active medications daily for cardiovascular disease (β blockers, ACE inhibitors, calcium channel blockers, diuretics, lipid-lowering agents), 10 had diabetes mellitus, and 2, who had undergone transurethral prostatectomy, were receiving 3 to 6 different active medications.

**Adverse effects:** Sildenafil citrate caused adverse effects in 73 patients. Thirty-two of them had a positive response to dimix, including 14 of 25 (56%) with facial flushing, 8 of 20 (40%) with headache, 7 of 7 (100%) with dizziness, 2 of 9 (22.2%) with tachycardia, and 2 of 4 (50%) with chest pain; the remaining patients responded to trimix.

The major adverse effect of the intracavernous injection was prolonged erection (up to 3 to 4 hours), which was noted in response to dimix in 25 of 248 patients (10%) after the first injection and in 19 of 135 (14.1%) after the second injection; this also occurred in 6 of 85 patients (7.1%) in response to trimix. In addition, small nodules during follow-up were noted in 9 of 135 patients (6.7%) after dimix, in 5 of 85 (5.9%) after trimix, and in 2 of 16 (12.5%) after quadmix; subcutaneous hemorrhage was noted in 3 of 16 patients (18.7%), and small nodules were noted in 2 patients (12.5%).

Prolonged erections due to intracavernous injection were treated by a decrease in the dosage of phentolamine. In patients with small nodules, treatment was stopped for 1.0 to 1.5 months during which vacuum therapy was used. The nodules disappeared within this period in all patients. For those with subcutaneous hemorrhage, injections were stopped for 1 to 2 weeks, and the dosage of papaverine and phentolamine was then decreased. The hemorrhage usually resolved after 2 to 3 weeks.

**Treatment of patients with contraindications for sildenafil citrate:** Fourteen patients (3.1%) were receiving long-term nitrate therapy (5 with uncontrolled hypertension, 7 with angina pectoris, and 2 with valvular disease and hypertension), of whom 8 (22.2%) responded to dimix and the remainder to trimix, all without adverse effects.

**Effect of cardiovascular drugs:** Of the 38 patients taking warfarin, 7 (18.4%) responded to sildenafil, 16 (42.1%) to dimix, 13 (34.2%) to trimix, and 2 (7.1%) to quadmix. Of the 15 patients who took digoxin, 8 (53.3%) responded to trimix, and 7 (46.7%) to quadmix. Two of the 15 (15.4%) had subcutaneous hemorrhage after trimix and 1 after quadmix during follow-up. Aspirin was not associated with adverse effects, with no differences noted between patients taking or not taking aspirin. Of the 48 patients who achieved a spontaneous erection, 46 (95.8%) were taking aspirin.

**DISCUSSION**

Thanks to its selective effect, sildenafil citrate is often used to treat ED in patients with cardiovascular disease. However, the reported results vary. Conti et al\(^4\) found a 70% improvement rate in patients with ischemic heart disease and Carson et al\(^13\) noted a 62.1% improvement in patients with ischemic heart disease and a 69.8% improvement in patients with hypertension. We administered sildenafil citrate in 417 patients with cardiovascular diseases, with a 49.2% positive response rate; specifically, 60.3% in patients with hypertension and 59.3% in those with coronary artery diseases. These relatively low rates may be explained by the age of our patients (36 to 91 years, mean 66.5 ± 4.5), variety of cardiovascular medications they were receiving, and the interventional procedures they underwent. Furthermore, >41.7% had severe ED according to the IIEF.

Thirty-six patients had contraindications to sildenafil citrate,\(^{10–12}\) including 11 (36.6%) with uncontrolled hypertension and/or angina pectoris, and 14 who had been using nitrate for a long time. We decided not to give the latter subgroup sildenafil citrate on the basis of the findings by Zusman et al\(^14\) showing that nitrates and nitric oxide donor drugs promote the formation of cyclic guanosine monophosphate by stimulating guanylate cyclase. Because sildenafil citrate also elevates cyclic guanosine monophosphate levels in smooth muscle, its coadministration with nitrates could lead to excessive reduction in blood pressure.

Of the 417 patients who received sildenafil 25 to 100 mg, 73 (17.5%) had serious side effects that

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**TABLE 4** International Index of Erectile Function Scores Before Treatment and After Two-year Follow-up

<table>
<thead>
<tr>
<th>ED Scores</th>
<th>Before Treatment</th>
<th>After 2-yr Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe, 1–10</td>
<td>48.2 ± 0.4%</td>
<td>14.4 ± 0.2%*</td>
</tr>
<tr>
<td>Moderate, 11–16</td>
<td>30.2 ± 0.5%</td>
<td>28.1 ± 0.3%</td>
</tr>
<tr>
<td>Mild-moderate, 17–21</td>
<td>12.6 ± 0.2%</td>
<td>30.4 ± 0.7%*</td>
</tr>
<tr>
<td>Mild, 22–25</td>
<td>5.7 ± 0.1%</td>
<td>36.7 ± 0.6%*</td>
</tr>
</tbody>
</table>

*p < 0.001; †p < 0.05.
warranted more careful treatment in 20: 9 (2.2%) had tachycardia (3 with controlled hypertension, 6 with arrhythmia and hypertension); 7 (1.7%) had dizziness (5 with hypertension and 2 with coronary artery disease); and 4 (1%) had chest pain (3 with stable angina pectoris and 1 after coronary artery bypass). Zusman et al\textsuperscript{14} reported a 0.2% rate of tachycardia. In their series, tachycardia, dizziness, and chest pain occurred in 20 patients with controlled hypertension and stable angina pectoris 5 years after coronary artery bypass surgery. Death after taking sildenafil was reported in 77 cases by Klone and Joraw,\textsuperscript{15} in 53 cases by Mittleman et al,\textsuperscript{16} and in 150 cases by Chew et al\textsuperscript{17} (all patients with cardiovascular disease).

Our success rates with the dimix, trimix, and quadmix were 54.4%, 75.2%, and 57.1%, respectively. This raises the question: why not administer trimix or quadmix directly after failure of sildenafil? We had several reasons for trying dimix first: (1) Both trimix and quadmix contain prostaglandin E1, which when injected intracavernously, may cause pain during erection in up to 11.7% to 80% of patients,\textsuperscript{18,19} (2) Trimix and quadmix require complicated preparation and storage. (3) Prostaglandin E1 needs to be purchased from an external source by our institution and is costly. (4) Quadmix is associated with more adverse effects, namely dizziness and plaque and subcutaneous hemorrhage, reported in 7% and 4% of patients, respectively, by Montorsi et al.,\textsuperscript{20} and small nodules after >12 months use, reported in 57% of patients by Levine et al.\textsuperscript{21} In the present study, when we began therapy with sildenafil and progressed to intracavernous injections with increasingly complex combinations of drugs, the rates of adverse effects were compared with earlier reports.\textsuperscript{18–24} After 2 years, dimix was associated with small nodules in 6.7% of patients, trimix was associated with small nodules in 5.9% and subcutaneous hemorrhage in 8.2% of patients, and quadmix was associated with small nodules in 12.5% and subcutaneous hemorrhage in 18.7% of patients. All patients with subcutaneous hemorrhage were taking warfarin.

Thus, the treatment program in patients with cardiovascular diseases, beginning with sildenafil citrate and dimix, produced a good positive response in patients with mild and mild-to-moderate ED. More complex compounds of vasoactive drugs, i.e., trimix, quadmix, sildenafil citrate + trimix (which gradually increased in dosage) and penile implants were more effective in patients with moderate and severe forms of ED.