Effect of Picotamide on the Clinical Progression of Peripheral Vascular Disease
A Double-Blind Placebo-Controlled Study

Francesco Balsano, MD; Francesco Violi, MD; and the ADEP Group*

Background. Patients with peripheral vascular disease (PVD) undergo a clinical course that can be complicated by cardiovascular events occurring in several areas of the circulation.

Methods and Results. In the present study we investigated the ability of picotamide, a substance that inhibits platelet thromboxane \( A_2 \) \( \left( \text{TXA}_2 \right) \) synthase and antagonizes \( \text{TXA}_2 \) receptors, to reduce cardiovascular complications in PVD patients. The study was double blind and placebo controlled. After a 1-month run-in period, 2,304 patients were randomly allocated to either placebo or picotamide (300 mg i.d.) and followed for 18 months. Major and minor events were analyzed. Results of an “intention-to-treat analysis” were that patients on picotamide suffered 45 major events (3.9%) and 77 minor events (6.7%), whereas those taking placebo suffered 52 major (4.5%) and 99 minor events (8.6%). There was borderline statistical difference between the two groups with respect to the sum of the major and minor events (risk reduction, 18.9%; \( p=0.056 \), log-rank test). Results of an “on-treatment analysis” were that patients on picotamide suffered 40 major (3.8%) and 66 minor events (6.3%), whereas those taking placebo suffered 45 major (4.2%) and 95 minor events (8.9%). The sum of both major and minor events was 106 (10.1%) in the picotamide group and 140 (13.1%) in the placebo group. This difference was significant (risk reduction, 23%; \( p=0.029 \), log-rank test).

Conclusions. The results of this study indicate that picotamide reduces cardiovascular complications in PVD patients. The apparently low effect of this drug in reducing major events suggests that further studies be made with picotamide in PVD patients who are at high risk of cardiovascular complications so as to further assess its clinical efficacy. (Circulation 1993;87:1563–1569)

Key Words • vascular disease, peripheral, thromboxane • cardiovascular disease • antiplatelet therapy

Patients with peripheral vascular disease (PVD) have a relatively benign clinical course; about 75% of them have stable symptoms, and only 5% undergo amputation over a period of 4–9 years.1 There is a growing body of evidence, however, that the clinical history of PVD is complicated by fatal and nonfatal vascular accidents occurring frequently in the cardiac and cerebral circulations.2,3 Over a 1-year follow-up period, about 6% of PVD patients may experience major vascular complications such as vascular death or nonfatal myocardial infarction (MI); another 10% may suffer from minor vascular events including angina, transient ischemic attack (TIA), or PVD deterioration.4 Platelets play an important role in progression of atherosclerotic disease. This has been definitively proved by clinical trials with antiplatelet drugs showing that this pharmacological approach reduces vascular death, MI, and stroke by 25%5 in a wide variety of patients at risk. The investigation of antiplatelet agents in PVD as a model to study the role of platelets in its clinical evolution has received less attention than other clinical models such as unstable angina, MI, or TIA. Two large clinical trials with antiplatelet agents have been published recently, in which ketanserin (PACK study)6 or ticlopidine (STIMS study)7 was given to PVD patients. Although the PACK study did not show any beneficial effect of ketanserin, the STIMS study showed that ticlopidine reduces vascular death caused by coronary heart disease. To assess further the effect of antiplatelet agents on the clinical evolution of PVD, we planned a randomized, double-blind, placebo-controlled study with picotamide, an antiplatelet drug with a dual mechanism of action. Picotamide, in fact, inhibits thromboxane \( A_2 \) \( \left( \text{TXA}_2 \right) \) synthase and antagonizes \( \text{TXA}_2 \) receptors.7,8

Methods

Study Design

The study was planned as a double-blind randomized multicenter trial stratified by center. Each center was expected to enroll 20 patients equally distributed between picotamide and placebo according to a completely randomized list. The randomization lists were generated by an automatic procedure developed expressly to have two balanced groups in each center. In all, 120 Italian centers participated in the study. After a single-blind run-in period of 1 month on placebo treat-
ment, patients were given either picotamide (300 mg t.i.d.) or placebo and followed up for 18 months. The effectiveness of the treatment was assessed by qualitative evaluation of selected major and minor events, validated under blinded conditions by an independent review committee.

Patients

The enrollment of patients started January 1, 1989, and closed August 30, 1989. During this period, all male and female patients up to 80 years old suffering from PVD were screened consecutively. PVD was defined according to one of the following criteria: 1) patients with claudication defined as leg pain on walking that disappeared in 5 minutes on standing and an ankle/arm pressure ratio by Doppler ultrasonography ≤0.85 in the posterior and anterior tibial artery of one foot; or 2) patients with claudication with previous amputation or reconstructive vascular surgery. The exclusion criteria were treatment with antiplatelet drugs such as aspirin, ticlopidine, diprydamole, indobufen or other nonsteroidal anti-inflammatory drugs, or anticoagulants; pain at rest; skin lesions; myocardial infarction, stroke, or surgical intervention in the previous 3 months; stable or unstable angina requiring aortocoronary bypass or angioplasty; liver insufficiency (prothrombin activity ≤40%); serious renal disorders (serum creatinine ≥2.8 mg%); and other conditions resulting in a life expectancy of <2 years.

Organization

After 1 month of run-in, during which patients were given placebo in single blind, patients who still satisfied the entry criteria were randomized to either placebo or picotamide treatment. The appearance and taste of the capsules were identical. Compliance with placebo during the run-in phase was verified by counting the remaining capsules. Patients were considered compliant if they took at least 75% of the prescribed dosage. Patients had clinical checkups 1, 3, 6, 9, 12, 15, and 18 months after enrollment. Blood for routine analysis was taken at 0, 6, and 12 months of follow-up. The routine investigations included red and white blood cell counts and assessment of hepatic (ALT, AST, etc.) and renal (serum creatinine, blood urea, etc.) function. The patients were queried about their consumption of capsules and reminded not to take any of the drugs listed in the explanatory pamphlet. No other drugs that affect platelet function or blood coagulation could be taken during the 18 months of the trial. If major or minor events occurred (as defined here), a special form with all the clinical documentation was sent in a sealed envelope to an independent review committee for validation. The statistical center received the same information by means of another sealed envelope and waited for the validation of the events by the executive committee. The record forms containing all other information were checked by independent trial monitors.

Outcomes

During the follow-up, we analyzed a series of major and minor events. Major events included 1) vascular and nonvascular death, 2) fatal and nonfatal MI, 3) fatal and nonfatal stroke, 4) amputation above the ankle for reasons other than tumor or trauma, and 5) excision of ischemic viscera. MI and stroke were considered fatal if death occurred within 1 month of the index event. Minor events included 1) recently developed angina or unstable angina, 2) possible or probable MI, 3) TIA, 4) minor stroke, 5) recently developed renal failure, 6) hypertension, and 7) deterioration of vascular disease leading to surgical intervention or angioplasty or local thrombolysis. The occurrence of any of the above minor events did not require treatment discontinuation. Each end point was defined precisely in the protocol. Each patient contributed only one event; if a patient had both a minor and a major event, only the latter was counted.

Sample Size

From the incidence of major and minor events observed in our country during the PACK study of untreated patients (14% in 18 months), we calculated that to detect a 25% relative reduction of the incidence of major and minor events with the active treatment using the log-rank test, the sample would have to be 1,100 patients in each group (α=0.05 and β=0.20, one-tailed test). To avoid the risk of a great number of patients being lost to follow-up, the number of patients enrolled was increased by 10%.

Statistical Analysis

Event-free analysis was performed, establishing survival curves according to the Kaplan-Meier method. The patients lost to follow-up and those who withdrew alive were considered as censored in this analysis. The null hypothesis $H_0: \theta = 1$, where $\theta$ is the odds ratio of the two curves, was tested by the log-rank test. The 95% confidence interval was also calculated. To perform this analysis, the Proc Lifetest was used (SAS 6.04).

Compliance

Compliance with the prescribed medication during the follow-up was verified by counting the remaining capsules at each visit. Patients were considered compliant if they took at least 75% of the prescribed dosage during the entire study.

Results

After the 1-month run-in period, a total of 2,304 patients were randomly allocated to receive either picotamide or placebo. The characteristics of the patients in the two groups were similar at the time of randomization (Table 1).

As expected, smoking, hypertension, dyslipidemia, and diabetes were the most common risk factors; 15.0% on picotamide and 12.7% on placebo had a clinical history of coronary heart disease, whereas 8.1% on picotamide and 7.1% on placebo had been suffering from cerebrovascular disease. Comparable percentages of patients (28.9% on picotamide and 28.7% on placebo) had previously undergone surgery or angioplasty for cardiovascular disease. Concomitant treatments were equally distributed in the two groups.

During the study, 116 patients were lost to follow-up, 57 (4.9%) on picotamide and 59 (5.1%) on placebo.
TABLE 1. Patient Characteristics at the Randomization Visit

<table>
<thead>
<tr>
<th></th>
<th>Picotamide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=1,150)</td>
<td>(n=1,154)</td>
<td></td>
</tr>
<tr>
<td>Age (years, mean±SD)</td>
<td>64.6±7.31</td>
<td>62.9±7.45</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>84.9</td>
<td>83.6</td>
</tr>
<tr>
<td>Female</td>
<td>15.1</td>
<td>16.4</td>
</tr>
<tr>
<td>Ankle/arm ratio (mean±SD)</td>
<td>0.68±0.14</td>
<td>0.69±0.13</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmokers</td>
<td>12.4</td>
<td>14.5</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>48.0</td>
<td>48.4</td>
</tr>
<tr>
<td>Smokers</td>
<td>39.6</td>
<td>37.1</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20.0</td>
<td>18.1</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>34.3</td>
<td>37.2</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>36.3</td>
<td>35.8</td>
</tr>
<tr>
<td>Hypertriglyceridemia (%)</td>
<td>30.6</td>
<td>29.4</td>
</tr>
<tr>
<td>Low serum HDL (%)</td>
<td>12.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Previous CHD (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>8.0</td>
<td>7.4</td>
</tr>
<tr>
<td>Angina</td>
<td>7.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Previous CVD (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>TIA</td>
<td>6.7</td>
<td>5.4</td>
</tr>
<tr>
<td>Concomitant diseases (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous arterial surgery or angioplasty</td>
<td>28.9</td>
<td>28.7</td>
</tr>
<tr>
<td>Concomitant therapies (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasodilators</td>
<td>21.2</td>
<td>20.1</td>
</tr>
<tr>
<td>Digitalis</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Diuretics</td>
<td>3.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Other antihypertensive drugs</td>
<td>7.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Insulin or oral hypoglycemics</td>
<td>5.6</td>
<td>5.5</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>0.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Antiulcer drugs</td>
<td>2.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Antidysslipidemic drugs</td>
<td>2.9</td>
<td>3.1</td>
</tr>
</tbody>
</table>

HDL, high density lipoprotein; CHD, coronary heart disease; MI, myocardial infarction; CVD, cerebrovascular disease; TIA, transient ischemic attack.

Withdrawal From the Trial

Forty-eight patients on picotamide (4.2%) and 29 (2.5%) on placebo were withdrawn from the study; 18 patients on picotamide and 13 on placebo were withdrawn because of side effects occurring predominantly in the gastrointestinal tract (Table 2).

Side Effects

Side effects occurred in 14.3% of patients on picotamide and 13.5% on placebo (Table 3). The most common were gastrointestinal disturbances, predominantly gastric pain (11.1% on picotamide and 12.0% on placebo). Routine laboratory investigations performed during and at the end of the study did not show any clinically relevant changes.

Compliance

Compliance averaged 98% for both treatments. No patient was excluded from the analysis because of <75% compliance.

Outcomes

The intention-to-treat analysis for major and minor events is reported in Table 4.

The sum of major and minor events was 122 (10.6%) in the picotamide group and 151 (13.1%) in the placebo group (risk reduction, 18.9%; p=0.056 at log-rank test). Five patients in the picotamide group and four in the placebo group died from noncardiovascular complications. Nine patients on picotamide and nine on placebo had more than one minor event.

Patients taking picotamide had 45 major events (3.9%) and 77 minor events (6.7%), whereas patients taking placebo had 52 major (4.5%) and 99 minor events (8.6%). According to the on-treatment analysis (Table 5), the sum of major and minor events was 106 (10.1%) in the picotamide group and 140 (13.1%) in the placebo group (risk reduction, 23%; p=0.029 at log-rank test). Patients taking picotamide had 40 major events (3.8%) and those taking placebo 45 (4.2%); minor events were 66 (6.3%) in the picotamide group and 95 (8.9%) in the placebo group.

The event-free analysis with survival curves is shown in Figure 1.

Discussion

The objective of the present trial was the evaluation of the clinical efficacy of a new antiplatelet agent in the cardiovascular complications occurring in patients with PVD. Picotamide interferes with the arachidonic acid cascade of platelets by inhibiting TxA2 synthase and antagonizing TxA2 receptors. Unlike aspirin, it does not affect cyclooxygenase. This research was planned according to the clinical suggestions of the largest trial performed in PVD patients, the PACK study, which indicated that over a period of 1 year, about 16% of patients may experience major and minor events. The results of our trial are at variance with this finding in that the rate of major and minor events was lower. Even if our trial had foreseen a rate of frequency of events lower than reported in the PACK study, the rate of major events is surprisingly low. In fact, <4% of patients suffered major events over 1 year of follow-up.
TABLE 4. Major and Minor Cardiovascular Complications in Patients Treated With Picotamide or Placebo for 18 Months: Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th></th>
<th>Picotamide (No.=1,150)</th>
<th>Placebo (No.=1,154)</th>
<th>Reduction of risk (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major + minor events</td>
<td>122 (10.6)</td>
<td>151 (13.1)</td>
<td>18.9</td>
<td>0.80 (0.63–1.01)*</td>
</tr>
<tr>
<td>Major events</td>
<td>45 (3.9)</td>
<td>52 (4.5)</td>
<td>13.2</td>
<td>0.86 (0.57–1.29)</td>
</tr>
<tr>
<td>Death</td>
<td>20 (1.7)</td>
<td>22 (1.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>13 (1.1)</td>
<td>16 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (0.7)</td>
<td>9 (0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>4 (0.3)</td>
<td>5 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>77 (6.7)</td>
<td>99 (8.6)</td>
<td>22.0</td>
<td>0.76 (0.55–1.04)</td>
</tr>
<tr>
<td>Angina</td>
<td>10 (0.9)</td>
<td>14 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable or possible MI</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>30 (2.6)</td>
<td>34 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor stroke</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT and pulmonary embolism</td>
<td>1 (0.1)</td>
<td>4 (0.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal failure or hypertension</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD deterioration</td>
<td>32 (2.9)</td>
<td>41 (3.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack; DVT, deep venous thrombosis; PVD, peripheral vascular disease.

*p=0.0565 (log-rank test).

This cannot be explained by a different frequency of common risk factors, which in fact was similar to that previously reported. It is noteworthy, however, that the clinical history of our patients showed a frequency of coronary heart disease, cerebrovascular disease, or surgery for arterial disease relatively lower than occurred in the PACK study. This suggests that in a PVD population, other risk factors should be studied to better understand this apparent discrepancy. Another possible explanation is that the inclusion criteria we chose selected a population with a different rate of atherosclerotic progression. The inclusion of patients with more severe PVD probably would have increased the rate of major complications.1,11 This study gave us the opportunity to have information on the clinical history of PVD and to assess the

TABLE 5. Major and Minor Cardiovascular Complications in Patients Treated With Picotamide or Placebo for 18 Months: On-Treatment Analysis

<table>
<thead>
<tr>
<th></th>
<th>Picotamide (No.=1,045)</th>
<th>Placebo (No.=1,066)</th>
<th>Reduction of risk (%)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major + minor events</td>
<td>106 (10.1)</td>
<td>140 (13.1)</td>
<td>22.8</td>
<td>0.76 (0.59–0.97)*</td>
</tr>
<tr>
<td>Major events</td>
<td>40 (3.8)</td>
<td>45 (4.2)</td>
<td>11.1</td>
<td>0.90 (0.58–1.39)</td>
</tr>
<tr>
<td>Death</td>
<td>17 (1.6)</td>
<td>18 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>13 (1.2)</td>
<td>15 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (0.7)</td>
<td>8 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputation</td>
<td>3 (0.3)</td>
<td>4 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor events</td>
<td>66 (6.3)</td>
<td>95 (8.9)</td>
<td>29.3</td>
<td>0.68 (0.49–0.95)</td>
</tr>
<tr>
<td>Angina</td>
<td>9 (0.9)</td>
<td>13 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probable or possible MI</td>
<td>0 (0.0)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>28 (2.7)</td>
<td>33 (3.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor stroke</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe renal failure or hypertension</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT and pulmonary embolism</td>
<td>1 (0.1)</td>
<td>4 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD deterioration</td>
<td>25 (2.4)</td>
<td>39 (3.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; MI, myocardial infarction; TIA, transient ischemic attack; DVT, deep venous thrombosis; PVD, peripheral vascular disease.

*p=0.029 (log-rank test).
clinical efficacy of picotamid in a relatively short period of time. By on-treatment analysis, we observed a significant reduction of major and minor events in patients treated with picotamide. In accordance with the PACK study, the event-free analysis indicated that about 1 year of treatment was necessary to observe differences between placebo and picotamide.

The small number of major events that occurred in both the treatment and placebo groups did not allow us to observe differences in this category of cardiovascular complications. This should be investigated in a further study, particularly in patients with a greater degree of risk for cardiovascular events than occurred in our study, to evaluate the full potential of such treatment.

The efficacy of antiplatelet treatment in the prevention of cardiovascular complications occurring in PVD patients has been analyzed in two previous large clinical trials.⁴⁶ Although the PACK study did not show any beneficial effect of ketanserin, the STIMS study showed that ticlopidine prevents cardiovascular complications. By intention-to-treatment analysis, the STIMS study showed 11.4% (p=0.24) reduction of vascular complications compared with 18.9% (p=0.056) in our trial; by on-treatment analysis, the STIMS study showed 38.4% (p=0.017) reduction of vascular complications compared with 22.8% (p=0.029) in our trial.

In conclusion, our study further indicates that the clinical history of PVD patients is complicated by cardiovascular events occurring in several circulatory territories. Picotamide is a well-tolerated drug and seems to protect against global cardiovascular complications occurring in PVD patients; it could be a candidate for future investigations to further assess its clinical efficacy.

Appendix

Atherosclerotic Disease Evolution by Picotamide (ADEP) Group


Italian Centers:
- Prof. Carlo Bracale, Dr. Bernardo Benedetto, Catte-
dra di Chirurgia Vascolare, Dir. p. G.C. Bracale, III Facoltà Medicina e Chirurgia, Università degli Studi di Napoli “Federico II.”
- Gregorio Brevetti, Sergio Perna, Dipartimento di Medicina Interna, IIl Facoltà Medicina e Chirurgia, Università degli Studi, Napoli.
- Prof. Vincenzo Coto, Manlio Cocozza, IVl Div. Medicina Interna, IIl Facoltà Medicina e Chirurgia, Università degli Studi, Napoli.
- Vincenzo Canonico, Prof. Franco Rengo, Cattedra di Geri-
atria, IIl Facoltà Medicina e Chirurgia, Università degli Studi, Napoli.
- Antonio De Donato, Maria Pia Mannelli, Serv. Chirurgia Vascolare, c/o Vl Chirurgia Generale, Ospedale “Cardarelli,” Napoli.
- Prof. Raffaele Del Guercio, Michele Del Guercio, Cattedra di Gera-
atria, IIl Facoltà Medicina e Chirurgia, Università degli Studi, Napoli.
- Angelo Michele Farina, Alfonso Marra, Il Divisione Chirur-
gia Generale, Sez. Chirurgia Vascolare (Resp. dr. m.A. Farina), Ospedale Civile, Caserta.
- Prof. Alberto Marcialis, Angelo Matarazzo, Cattedra di Chirurgia Vascolare, Il Facoltà Medicina e Chirurgia, Dir. p. A. Marcialis, Università degli Studi, Napoli.
- Prof. Domenico Policicchio, Dr. Renato Tizzano, Dr. Efrem Pirmatteo, Day Hospital Geriatrico, USL 4 Avelino.
- Dr. Matteo Impaglialetti, Ospedale Servizio di Angiologia, Casa Sollievo della Sofferenza, S. Giovanni Rotondo, Foggia.
- Prof. Guido Regina, Dr. Antonio Lillo, Istituto Chirurgia Vascolare Generale, Policlinico, Bari.
- Dr. Vincenzo Limosano, Aiuto Divisione Chirurgia Vasco-
lare, Ospedale di Carbonara, Bari.
- Dr. Sica, Assistente, Istituto Chirurgia Vascolare, Primario Prof. Odero, Policlinico, Bari.
- Prof. Nicola Tomassini, Dr. Fernando Manes, Divisione Chirurgia Generale, Ospedale Generale Provinciale C.G. Mazzoni, Ascoli Piceno.
- Prof. Filippo Altilia, Dr. Claudio Crisostomi, Divisione Medicina Generale, Ospedale Generale Provinciale C.G. Mazzoni, Ascoli Piceno.
- Prof. Carlo Spartera, Dr. Giuseppe Morettini, Cattedra Chirurgia Vascolare, Università degli Studi L’Aquila, Ospedale S. Salvatore, L’Aquila.
- Dr. Vincenzo Lamensa, Dr. Antonio Manente, Istituto di Semioetica Medica, Università degli Studi Chieti, Ospedale S.S. Annunziata, Chieti.
- Prof. Vittorio Saba, Dr. Piergiorgio Constantini, Semeiotica Chirurgia Università degli Studi Ancona, Ospedale S. Croce, Fano Pesaro.
Dr. Mauro Bavosi, Dr. Paolo Quagliarini, Divisione Chirurgica Generale, Ospedale Civile Senigallia Ancona.
Prof. Franco Santucci, Dr. Carlo Bartocchini, Unità Organica di Medicina Ospedale “R. Silvestrini,” S. Andrea delle Fratte, Perugia.
Prof. Luigi Moggi, Dr.ssa Maria Antonietta Puglia, II Clinica Chirurgica Università degli Studi Perugia, Ospedale Policlinico, Perugia.
Prof. Salvatore Occhipinti, Dr. Gabriele Pagliariccio, Clinica Chirurgica Università degli Studi Ancona, Ospedale Generale Regionale Torrette, Perugia.
Prof. G.M. Andreotti, Prof. S. Signorelli, Cattedra Angiologia Ospedale Garibaldi, Catania.
Prof. Rosario Bonaccurso, Dr. Salvatore Cavallaro, Istituto Chirurgia Vascolare Ospedale Garibaldi, Catania.
Prof. Giuseppe Squadrato, Prof. Antonio Saitta, Dipartimento di Medicina Interna, Policlinico, Messina.
Prof. Maurizio Basile, Dr. Vitale Reso Mattace, I Clinica Chirurgica Policlinico, Messina.
Prof. Emidio Feraco, Istituto Nazionale di Ricerca e Cure per Anziani (I.N.R.C.A.), c/o Muoio Piccolo, Cosenza.
Prof. G. Licata, Dr. G. Merlino, Cattedra di Patologia Speciale Medica e Metodologia, Clinica II, Università degli Studi, Palermo.
Prof. G.B. Bombiani, Dr. G. Avello, Cattedra di Clinica Medica Generale e Terapia Medica, Università degli Studi, Palermo.
Prof. A. Notarbartolo, Dr. M. Belvedere, Cattedra di Patologia Speciale Medica e Metodologia, Clinica III, Università degli Studi, Palermo.
Prof. S. Di Blasi, Dr.ssa M.M. D’Alessandro, Istituto di Medicina Interna e Geriatria, Università degli Studi, Palermo.
Prof. V. Abadessa, Dr.ssa R. Perricone, Cattedra di Ematologia, Università degli Studi, Palermo.
Prof. M. Cospite, Dr. G. Millo, Dipartimento di Discipline Chirurgiche ed Anatomiche, Sez. di Angiologia, Università degli Studi, Palermo.
Prof. F. Cortese, Dr. F.D. Palumbo, Cattedra di Fisiopatologia Angiochirurgica, Dipartimento di Discipline Chirurgiche ed Anatomiche, Università degli Studi, Palermo.
Prof. D. Lo Bosco, Dr. M. Scialabba, Cattedra di Patologia Chirurgica, Università degli Studi, Palermo.
Prof. Elsa Marchitelli, Servizio Angiologia, Ospedale S. Eugenio, Roma.
Dr.ssa Rita Ramacci, Dr.ssa Celestina Iovino, Chirurgia Vascolare, Ospedale S. Filippo Neri, Roma.
Prof. Claudio Allegra, Dr.ssa Mariella Carioti, Reparto Angiologia, Ospedale San Giovanni, Roma.
Dr. Alessandro Andrianis, Dr. Pierluigi Rinaldi, Divisione di Medicina, Servizio di Ematologia, Ospedale S. Giaconio, Roma.
Prof. Fabrizio Benedetti Valentini, Dr. Salvatore Venosi, III Cattedra Chirurgia Vascolare, Università “La Sapienza,” Policlinico Umberto II, Roma.
Prof. Enrico Bologna, Dr. Paolo Traietti, Reparto di Medicina Ospedale Fatebenefratelli, Roma.
Prof. Sante Camilli, Dr. Giorgio Guarnera, Chirurgia Vascolare, Ospedale I.D.I., Roma.
Prof. Maurizio Caratelli, Dr. Lorenzo Risa, Chirurgia Vascolare, Ospedale Velletri, Roma.
Prof. Antonino Cavallaro, Dr. Luca Di Marzo, II Fisiopatologia Chirurgica, Università “La Sapienza,” Policlinico Umberto II, Roma.
Prof. Vincenzo Di Giovanni, Dr.ssa Rosa Colli, Istituto di Semeiologia Chirurgica, Scuola di Specializzazione Chirurgia Vascolare, Università Cattolica Sacro Cuore, Policlinico Gemelli, Roma.
Prof. Paolo Fiorani, Dr. Egizio Colella, I Cattedra Chirurgia Vascolare, Università “La Sapienza,” Policlinico Umberto II, Roma.
Prof. Domenico Melina, Dr. Furio Colivicchi, Istituto Patologia Medica, Università Cattolica Sacro Cuore, Policlinico Gemelli, Roma.
Prof. Gino Gambassi, Dr. Marcello Anti, Cattedra Clinica Medica, Università Cattolica Sacro Cuore, Policlinico Gemelli, Roma.
Prof. Luigi Gioffrè, Dr. Marcello Corsi, Servizio speciale Chirurgia, IV Clinica Chirurgica, Università “La Sapienza,” Policlinico Umberto II, Roma.
Dr. Mariano Garofalo, Dr. Paolo Albano, Chirurgia Vascolare, Clinica Città di Roma, Roma.
Prof. Giuseppe Mastroberardino, Dr.ssa M. Teresa Sciriti, Reparto Medicina, Clinica Villa Bianca, Roma.
Prof. Antonino Musca, Dr. Illo Cammarella, Reparto di Medicina, Policlinico Militare Celio, Roma.
Prof. G. Raimondo Pistolese, Dr. Arnaldo Ippoliti, Cattedra Chirurgia Vascolare, Università Tor Vergata, Roma.
Prof. Paolo Pola, Dr.ssa Angela Fazio, Cattedra di Metodologia Clinica Medica, Divisione Angiologia, Università Cattolica Sacro Cuore, Roma.
Prof. Marco Servi, Dr. Massimo Germani, II Divisione Geriatria, Ospedale Dell ’Addolorata, Roma.
Prof. Antonio Strano, Dr. Valerio Sangiulini, Dipartimento Medicina Interna, Università Tor Vergata, Roma.
Prof. Giovanni Brotzu, Dr.ssa Palmina Petruzzi, Istituto di Patologia e Chirurgia, Cattedra di Chirurgia Vascolare, Università degli Studi, Cagliari.
Dr. Inga Corrado, Dr. Riba Ugo, Servizio Angiologia, Ospedale Mauriziano Umberto II, Roma.
Dr. Rosti Giuseppe, Dr.ssa Ansaldi Egle, Centro Antidiabetico, II Medicina Generale, Ospedale Civile di Alessandria.
Prof. Ghilardi Fulvio, Dr. Berta Enrico, Centro Studio Malattie Vascolari, Clinica Bernini, Torino.
Prof. Fabrizio Fabbris, Dr. Massimo Neirotti, Istituto di Medicina e Chirurgia Geriatria, Ospedale Maggiore S. Giovanni Battista, Università degli Studi di Torino.
Dr. Giovanni Anfossi, Divisione Diabetologia, Ospedale S. Luigi Gonzaga, Orbassano, Torino.
Dr. Domenico Palombo, Dr.ssa Carla Porta, Dr. Marco Udini, Unità di Chirurgia Vascolare ed Angiologia, Ospedale Regionale della Valle D’Aosta.
Prof. Domenico Bertini, Prof. Carlo Pratesi, Cattedra di Chirurgia Vascolare, Università di Firenze, Firenze.
Prof. Piero Cinelli, Prof. Silvano Citi, Centro Cardiologico Clinica Medica IV, Università di Firenze, Firenze.
Prof. Giuseppe Nuzzacci, Dr.ssa Nicolina Cavallaro, Cattedra di Angiologia, Università di Firenze.
Prof. Carlo Corsi, Dr. Carlo Cipriani, Unità Funzionale Cardio-Angiologica, S. Chiara, Firenze.
Dr. Shlomo Gimel, Dr. Maurizio Felice, U.O. di Cardiologia, Nuovo Ospedale S. Giovanni di Dio, Firenze.
Dr. Marco Grazzini, Dr. Giovanni Mantini, Div. Cardiologia, Ospedale S. Giovanni Valdarno, Arezzo.
Dr. Giuseppe Di Silvestro, Dr.ssa Maurizia Spillantini, U.O. di Medicina Ospedale di Sansepolcro, Arezzo.
Prof. Federico Bartolomei, Dr. Daniele Righi, U.O. di Medicina III, Ospedale di Pistoia, Pistoia.
Prof. Costantino Giusti, Dr.ssa Maria Teresa Caputo, U.O. di Medicina III, Università di Pisa, Pisa.
Prof. Franco Mosca, Dr. Mauro Ferrari, U.O. di Chirurgia Generale e Vascolare di Pisa, Pisa.
Dr. Alfonso Lagni, Dr. Pier Luigi Vannucchi, U.O. di Medicina, Ospedale S. Maria Nuova, Firenze.
Prof. Mario Rubegni, Dr. Daniele Provetti, U.O. di Geriatria, Ospedale S. Maria della Scala, Siena.
Prof. Tullio Di Perri, Prof. Alberto Autieri, Clinica Medica, Università di Siena, Siena.
Prof. Antongiulio Dettori, Dr. Alessandro Megha, VI Divisione Medica, Ospedale Di Parma, Parma.
Dr. Alfio Moratti, Dr. Mauro Paolichelli, Divisione di Angiologia, Ospedale di Reggio Emilia, Reggio Emilia.
Acknowledgments

We are grateful to Drs. G. Ciminì and P. Graziani for their fruitful collaboration and to P. Taglioni for editing the manuscript.

References

F Balsano and F Violi

Circulation. 1993;87:1563-1569
doi: 10.1161/01.CIR.87.5.1563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/5/1563

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/