Secondary Prevention of Stroke in Italy
A Cross-Sectional Survey in Family Practice

Alessandro Filippi, MD; Angelo Antonio Bignamini, PhD; Emiliano Sessa; Fabio Samani, MD; Giampiero Mazzaglia, MD, PhD, MSc

Background—Hypertension control and antiplatelet or oral anticoagulant drugs are the basis for secondary prevention of cerebrovascular events. Family physicians (FPs) are usually involved in both aspects of prevention, but no research has been carried out in Italy to evaluate the behavior of FPs in this field of prevention.

Methods—Data concerning 318 Italian FPs and 465 061 patients were extracted from the Health Search Database. Patients with coded diagnoses of stroke and transient ischemic attack (TIA) were selected. Demographic records and information regarding presence of concurrent disease and medical records were also obtained. Logistic regression analyses were carried out to assess whether conditions exist that make appropriate control of blood pressure (BP) and prescription of antiplatelet or anticoagulant drugs more likely.

Results—We selected 2555 patients with diagnosis of stroke and 2755 with TIA. Among all of the subjects, 32.6% had no BP recorded. Among the remaining subjects, 58.7% reported uncontrolled BP. Isolated systolic hypertension has been shown in 68.8% of patients with uncontrolled BP. Antiplatelet and anticoagulant drugs were prescribed in 72% of these cases. Factors that made the prescription significantly more unlikely were diagnosis of TIA (odds ratio [OR], 0.47; 95% confidence interval [CI], 0.41 to 0.54), total invalidity (OR, 0.66; 95% CI 0.56 to 0.78), and time from event of 5 years or more (OR, 0.81; 95% CI, 0.70 to 0.94).

Conclusions—Italian FPs could improve secondary prevention of cerebrovascular accidents. The primary target of intervention should be the control of systolic BP, and the group of patients with unacceptably high BP should be given priority. All of these patients should have been prescribed antiplatelet drugs or anticoagulant agents, except in cases of extremely short life expectancy or substantial contraindications. (Stroke. 2003;34:000-000.)

Key Words: cerebrovascular accident □ family practice □ prevention

Stroke is the third leading cause of mortality and the first cause of disability in Italy. The risk of recurrence is high after ischemic stroke and transient ischemic attacks (TIAs). Effective, albeit partial, secondary prevention is possible, and both national1 and international2,3 guidelines strongly recommend lowering high blood pressure (BP) and using either antiplatelet drugs or oral anticoagulants (OAs) when thromboembolism is suspected.

Although it is well known that implementation of guidelines in clinical practice is far from being complete, in Western countries antihypertensive and antiplatelet drugs and OAs are usually prescribed for prevention purposes by family physicians (FPs).

However, data about secondary prevention of stroke in family practice are still scarce and, as far as we know, nothing is known about this issue in Italy. This information is crucial to planning intervention aimed at improving performance of FPs and, consequently, to reducing the recurrence of cerebrovascular disorders. We therefore decided to examine antihypertensive treatment and prescription of antiplatelet drugs and OAs among patients with a recorded diagnosis of cerebrovascular events.

Data Source
Data were obtained from the Health Search Database (HSD), which was set up by the Italian College of General Practitioners. Briefly, the HSD started recruiting FPs in 1998, and it was primarily aimed at carrying out observational studies of incidence and prevalence and studies on drug safety and prescription. The HSD currently contains information from >550 FPs with a patient population of >800 000. The participating FPs use the same software to record data during their daily practice, and they agreed to send periodically complete, but anonymous, records of their patients to the HSD. The FPs are selected to be representative of the whole Italian population. The information recorded includes patient demographics, medical diagnoses coded according to the ninth edition of International Classification of Diseases (ICD-9), drug prescriptions coded according to the Anatomical Chemical classification system, hospital referrals, and diagnostic investigations with their relevant values.
Patient Selection

For the purpose of this study, we considered 318 FPs with a patient population of 465,061 individuals. We then selected prevalent cases with a coded diagnosis of stroke (ICD-9 codes 434.9, 438, 438.0, 342, 342.0, 342.1, and 342.9) or encoded medical problems described as “stroke,” “hemiparesis,” or “hemiplegia” recorded in the HSD until December 31, 2001. We have also selected patients with a coded diagnosis of TIA (ICD-9 code 435).

For each patient, the following information was included: age, sex, year of first-ever event, presence of concurrent diseases (ie, diabetes, acute myocardial infarction [AMI], atrial fibrillation, and recognized total invalidity), systolic BP (SBP), and diastolic BP (DBP).

We have also obtained information regarding the following established therapies (we defined as “established” those therapies that had been prescribed at least twice in the last 6 months from the time of diagnosis): β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II antagonists, diuretics, calcium antagonists, aspirin and other antiplatelet agents, and anticoagulant therapy. Hypertension control was classified according to the following criteria: (1) optimally controlled, SBP <130 mm Hg and DBP <80 mm Hg; (2) acceptably controlled, SBP <140 mm Hg and DBP <90 mm Hg; (3) uncontrolled, SBP ≥140 mm Hg or DBP ≥90 mm Hg; and (4) unacceptably uncontrolled, SBP >160 mm Hg or DBP >100 mm Hg.

Statistical Analysis

Logistic regression analyses were carried out to assess whether conditions exist that make it more likely to obtain an appropriate control of BP and prescription of antplatelet drugs or OAs. Such analyses were tested according to the various patient characteristics and treatments applied. In the first analysis, testing BP control, multiple-category variables (ie, age, years from event, or number of coprescribed medications) have been iteratively analyzed and collapsed to dichotomous variables. Interactions between factors were instead not tested, to avoid empty or sparsely populated cells.

The model therefore included as prognostic factors the following categories: diagnosis (ie, stroke or TIA); sex; age (ie, <65 or ≥65 years); time from event (ie, <3 or ≥3 years); and presence of concurrent diseases such as diabetes, AMI, and atrial fibrillation. As treatments the total number of medications prescribed were classified as none and 1 or more.

In the second analysis, testing OA use, the final model included as prognostic factors the following categories: diagnosis (ie, stroke or TIA); sex; age (ie, <65 or ≥65 years); time from event (ie, <5 or ≥5 years); presence of concurrent diseases such as recognized total invalidity, diabetes, history of AMI or atrial fibrillation; and number of other concurrent medications (ie; none, 1, or more). Statistical analysis was performed by using SPSS version 10.1 (SPSS Inc).

Results

The total sample included 2555 patients diagnosed with stroke and 2755 with TIA. The main demographic and clinical characteristics of the sample are reported in Table 1.

Control of BP

Overall, records of 32.5% of the sample under study had no information recorded regarding BP control. In patients with previous cerebrovascular events, hypertension can be considered optimally controlled when kept below 130/80 mm Hg. However, for a series of practical reasons, a level below 140/90 mm Hg can be considered acceptable under most circumstances. The degree of BP control is reported in Table 2. Table 3 shows the degree of systolic and diastolic control, with uncontrolled SBP in 57.4% of patients and uncontrolled DBP in 18.5%. The overall poor control of BP did not appear to be a result of the number of antihypertensive agents used (Table 4). Thus, we determined that the reasons for the lack of control should be investigated on the basis of the type, rather than the number, of treatments used. However, as clearly shown in Table 5, there was no indication that any of the monitored therapeutic classes has any substantially greater effect than any other in facilitating the control of BP.

To find out whether there are conditions leading to an appropriate BP control, we tested the various prognostic factors and treatments applied with logistic regression analysis. Overall, the binomial logistic model fits the data quite well (Hosmer and Lemeshow test, NS), but it fails to explain a sizeable proportion of the variation in response (61.1% correctly classified), probably because several important variables were not available for testing (eg, compliance).

The following factors were predictive of control of BP: (1) history of myocardial infarction (odds ratio [OR], 1.38; 95% confidence interval [CI], 1.04 to 1.84) and (2) male sex (OR, 1.30; 95% CI, 1.13 to 1.49). The following factors are, instead, predictive of uncontrolled BP: (1) time since the event of ≥3 years (OR, 0.87; 95% CI, 0.76 to 0.99), (2) diagnosis of TIA (OR, 0.78; 95% CI, 0.67 to 0.90), (3) age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stroke (%)</th>
<th>TIA (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled</td>
<td>642 (42.5)</td>
<td>837 (40.5)</td>
<td>1479 (41.3)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>870 (57.5)</td>
<td>1232 (59.5)</td>
<td>2102 (58.7)</td>
</tr>
<tr>
<td><strong>Detailed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Optimal</td>
<td>156 (10.3)</td>
<td>236 (11.4)</td>
<td>392 (10.9)</td>
</tr>
<tr>
<td>Acceptable</td>
<td>486 (32.1)</td>
<td>601 (29.0)</td>
<td>1087 (30.4)</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>615 (40.7)</td>
<td>863 (41.7)</td>
<td>1478 (41.3)</td>
</tr>
<tr>
<td>Unacceptable</td>
<td>255 (16.9)</td>
<td>369 (17.8)</td>
<td>624 (17.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1512</td>
<td>2069</td>
<td>3581</td>
</tr>
</tbody>
</table>

*P value 0.749; †P value 0.219.
The influence of atrial fibrillation is borderline to significance \((P = 0.052)\) and is predictive of better control \((\text{OR}, 1.24; 95\% \text{ CI}, 0.99 \text{ to } 1.54)\).

**Use of Antiplatelet and Anticoagulant Agents**

Overall, 27.9\% \((95\% \text{ CI}, 27\% \text{ to } 29\%)\) of patients received neither antiplatelet drugs nor OAs. Among treated patients, 62.6\% \((95\% \text{ CI}, 61\% \text{ to } 64\%)\) used antiplatelet drugs, 5.8\% \((95\% \text{ CI}, 5\% \text{ to } 7\%)\) OAs, and 3.7\% \((95\% \text{ CI}, 3\% \text{ to } 4\%)\) both. Among patients being treated with both types of drugs, 45.9\% had a diagnosis of atrial fibrillation.

To find out which factors may influence the prescription of these agents, we tested the various available factors with the logistic regression analysis as indicated above. Overall, the binomial logistic model fits the data quite well \((\text{Hosmer and Lemeshow test, NS})\) and is statistically significant \(\left(\text{Cox and Snell} \ r^2 = 0.123; \text{Nagelkerke} \ r^2 = 0.178\right)\), but still it fails to explain a sizeable proportion of the variability in prescribing \((\text{percentage correctly attributed}, 74\%)\), probably because of some collinearity between variables.

The following factors were significantly related to prescription: (1) having prescribed at least another drug \((\text{OR}, 3.25; 95\% \text{ CI}, 2.84 \text{ to } 3.71)\); (2) presence of concurrent diseases such as atrial fibrillation \((\text{OR}, 2.54; 95\% \text{ CI}, 1.96 \text{ to } 3.29)\), AMI \((\text{OR}, 2.13; 95\% \text{ CI}, 1.47 \text{ to } 3.07)\), or diabetes \((\text{OR}, 1.47; \text{CI}, 1.24 \text{ to } 1.74)\); age \(\geq 65\) years \((\text{OR}, 1.57; 95\% \text{ CI}, 1.34 \text{ to } 1.84)\); and male sex \((\text{OR}, 1.39; 95\% \text{ CI}, 1.22 \text{ to } 1.58)\).

Instead, the following factors were significantly and negatively related to the prescription: (1) diagnosis of TIA \((\text{OR}, 0.47; 95\% \text{ CI}, 0.41 \text{ to } 0.54)\), total invalidity \((\text{OR}, 0.66; 95\% \text{ CI}, 0.56 \text{ to } 0.78)\), and time since event \(\geq 5\) years \((\text{OR}, 0.81; 95\% \text{ CI}, 0.70 \text{ to } 0.94)\).

**Discussion**

After ischemic stroke, the risk of recurrence is estimated at 10\% to 15\% in the first year and 4\% to 9\% per year in the first 5 years. After a TIA, the risk of stroke varies from 7\% to 12\% in the first year and from 4\% to 9\% per year in the first 5 years.\(^1\) For such reasons, the use of antiplatelet drugs and OAs is strongly recommended for secondary prevention according to several sets of guidelines.\(^1–3\) Moreover, it is well known that hypertension is largely undertreated\(^7\) and that antiplatelet drugs are under-used in high-risk patients.\(^4,8,9\)

We used the HSD to evaluate secondary prevention management of subjects with a registered diagnosis of stroke or TIA. No attempt was made to validate the diagnosis, because we had no interest in epidemiological evaluation, but only in assessing the attitude of Italian FPs after the diagnosis of cerebrovascular events had been made. Probably a few strokes and, possibly, even more TIAs may not have been confirmed after record review, but the FPs were at least sure enough of the diagnosis to record it in their computers and to manage the patients accordingly.

**Control of BP**

The first striking observation is that almost one third of patients had no BP measurement recorded. The probable presence of subjects who do not have access to their FPs’...
offices cannot explain the magnitude of this phenomenon, because only 332 of the 1729 patients without BP measurement were totally invalid. It is possible that some patients had their BP measured but not recorded. However, the widespread lack of recorded measurement seems to be compatible with underestimation of the relevance of hypertension as a modifiable risk factor.

In the remaining 3581 patients, BP was not controlled (≥140/90 mm Hg) in 58.7%, of whom 17.4% had “unacceptable” high values (SBP >160 mm Hg or DBP >100 mm Hg). As expected, in our rather old population, there were more isolated cases of uncontrolled SBP (57.4%) when compared with DBP. The problem of SBP control is not new, and it is particularly important for middle-aged and elderly hypertensive patients.

In the United States, for example, DBP but not SBP is controlled in 66.1% of patients 45 to 64 years of age and in 87.6% of patients ≥65 years of age. The percentage of “controlled” subjects is almost twice that of the general hypertensive population, which indicates greater, but still insufficient, attention to this risk factor.10

This is not surprising, because little research has been carried out on the secondary prevention of stroke. The only study published recently demonstrated that among individuals with previous stroke or TIA a flexible BP-lowering regimen, with perindopril for all patients and indapamide for angiotensin II antagonists, may be appropriate for elderly people who are badly needed.

Our first approach to understanding the reasons for the overall poor BP control was to find out whether there was any preclusion to the use of a sufficient number of antihypertensive agents, but this appears not to be the case. The percentage of patients with controlled BP is almost the same in the groups treated with 1, 2, 3, and 4 or more drugs.

Because isolated systolic hypertension is common, fear of excessive and dangerous lowering of DBP could hinder a more intense therapy, but the number of patients with very low DBP was so small (data not shown) that this problem cannot be considered relevant. We have no information about compliance. Therefore, it is possible that not all of the prescribed medicines were actually taken, “blunting” the increased effects of multiple prescriptions. We have no clear explanation for these data, but our favorite hypothesis is that FPs always accept the same suboptimal BP levels, and more drugs are needed because subjects with a progressively higher degree of resistance to treatment and/or severity of hypertension compose the 4 groups.

The identification of the safest and most effective antihypertensive treatments for the prevention of recurrent stroke is also uncertain, and our data confirmed no significant differences in BP control among the different types of antihypertensive prescribed. These results are consistent with previous studies, in which BP-lowering drugs in hypertensive patients, mostly without cerebrovascular disease, reduced the risk of initial stroke by about one third,12 with no large differences apparent between the main drug classes.13

Whatever the cause of poor BP control, according to our survey, substantial improvement in BP level is necessary. According to the World Health Organization guidelines,14 lowering BP by 10/5 mm Hg in this high-risk population could eliminate >10 cardiovascular events per 1000 person-years. If we optimistically suppose that BP control among subjects without any recorded value is not different from that observed among patients with recorded values, >46 events could be fairly easily avoided every year by better hypertension control. According to these data, >4600 events could be avoided every year in Italy, and this figure could probably double with optimal BP control.14,15

It is clear that new therapeutic strategies aimed mainly at controlling systolic hypertension in high-risk middle-aged and elderly people are badly needed.

### Use of Antipatelet and Anticoagulant Agents

All of the patients considered in this sample should have been prescribed antiplatelet or anticoagulant agents, unless there were substantial contraindications.1 Even if adherence to guidelines is fairly good (72% treated), overall, more than one quarter of patients were not treated with antiplatelet or with anticoagulant agents. In other words, almost 3 out of 10 patients with a history of stroke or TIA were not managed by the attending FPs according to the current recommendations. These results are better than those reported in other surveys on high-risk-patients in family practice9 but are still unsatisfactory. It is rather difficult to believe that 28% of patients monitored by FPs exhibit absolute or relative contraindications to treatment with antiplatelet agents. It is also unlikely that patients’ refusal, the only other option, could justify such a high percentage of underprescription.

It should be concluded that the FPs’ awareness of the current guidelines is still unsatisfactory, or that there are unclear hindrances in following the guidelines. To address this problem, we performed a logistic analysis, reported

### TABLE 5. Distribution of Blood Pressure Control by Type of Antihypertensive Prescribed

<table>
<thead>
<tr>
<th>Medication Prescribed</th>
<th>Stroke (n=1512)</th>
<th>TIA (n=2069)</th>
<th>Total (n=3581)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controlled</td>
<td>Uncontrolled</td>
<td>Controlled</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>80 (35.1)</td>
<td>148 (64.9)</td>
<td>63 (33.3)</td>
</tr>
<tr>
<td>Angiotensin II antagonists</td>
<td>84 (37.3)</td>
<td>141 (62.7)</td>
<td>76 (32.6)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>384 (37.9)</td>
<td>630 (62.1)</td>
<td>363 (35.9)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>323 (36.4)</td>
<td>564 (63.6)</td>
<td>233 (35.8)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>200 (36.3)</td>
<td>351 (63.7)</td>
<td>167 (36.1)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
above. Positive prescription predictors, in order of decreasing OR, were prescription of another medication, history of atrial fibrillation, history of AMI, history of diabetes, age ≥65 years, and male sex, whereas negative predictors, in order of decreasing OR, were time from event of ≥5 years, total invalidity, and diagnosis of TIA.

Overall, these factors are not completely unexpected. Elderly patients are also known to be more likely to follow the prescription, and because one does not write a prescription knowing beforehand that it will not be followed, known compliance also favors the prescription of a new drug (see also the largely favorable effect of having already prescribed at least another drug). Belonging to a high-risk group seems to be the most important factor for prescription: male sex, diabetes, older age, and previous AMI and atrial fibrillation are all positively correlated with prescription of antiplatelet/anticoagulant drugs. This is probably why TIA is associated with a lower prescription, because the risk of a new stroke is lower for those with TIA than for those with previous stroke. It is probable that this relatively small difference is overestimated by FPs. Also not unexpected is the significantly negative effect of the time from the event, given that the longer the time without cerebrovascular events, the lower the probability of their recurring. The negative influence of being recognized totally invalid on the probability of prescription is difficult to explain. The most probable hypothesis seems to be a negative judgment about the value of prophylaxis in severely disabled subjects. If this were true, it would be important to address the ethical aspects of treatment and non-treatment in highly disabled subjects. Because more than a quarter of patients do not receive prophylactic therapy, efforts to improve adequate prescription seem to be required, and the first target of intervention should be the patients with TIA, because they are twice as likely as patients with stroke not to receive antiplatelet/anticoagulant drugs. A possible useful approach could be the use of automatic computerized reminders, which could help FPs to increase appropriate prescriptions for secondary prophylaxis.

Some of the limitations of our survey have already been mentioned; others can be related to the selection of the FPs who delivered the data. It is possible, albeit improbable, that their therapeutic approach to secondary prevention is different from that of the general population of Italian FPs, because the participant FPs tried to keep accurate records of their professional activities and could be more aware of underperformance. If this were true, our data should be biased in favor of better treatment and the possibility of improvement should be larger than that indicated by our study.

Conclusions

Secondary prevention of cerebrovascular accidents among Italian FPs should be substantially improved. Even if BP control among patients with previous cerebrovascular events is almost twice as effective as among the general hypertensive population, in 60% of cases BP is not adequately lowered, causing thousands of potentially avoidable cardiovascular events every year. The primary target of intervention should be the SBP, and a special priority should be the group of patients with an unacceptably high BP, i.e., 17.4% of the whole sample in our survey. New therapeutic strategies are probably needed to address these problems in family practice.

All of these patients should have been prescribed antiplatelet or anticoagulant agents, except in cases of extremely short life expectancy or substantial contraindications.

It is rather unlikely that these conditions were present in more than one fourth of patients. Additional efforts must be made to better understand why so many patients are denied therapy and to develop new tools to help FPs to improve secondary prevention.

References

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