Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia and is also a strong independent risk factor for both systemic embolism and stroke (1,2). Since 1989, several randomized studies on stroke prevention (3) have tested two antithrombotic agents: warfarin and aspirin. Some meta-analyses (4–6) showed that warfarin decreases stroke by 62% compared with placebo. In studies where a statistical benefit with aspirin has been shown, this benefit is much less than seen with warfarin, with fewer bleeding complications and easier monitoring (4). In order to reduce both thromboembolic and bleeding events, the combination of low-dose warfarin and aspirin was investigated in three trials (7–9). All concluded that this combination therapy with an international normalized ratio (INR) below 1.5 was ineffective.

Theoretically, the combination of therapeutic doses of anticoagulant and antiplatelet agents (i.e., combined therapy) should have additional benefits and, recently, the Warfarin Aspirin Re-Infarction Study (WARIS) II found it superior to aspirin alone in the prevention of vascular events after myocardial infarction (MI) (10). Our trial has evaluated, for the first time, the efficacy and safety of this combination compared with one antiplatelet or anticoagulation alone in nonvalvular AF and in patients with mitral stenosis.

PATIENTS AND METHODS

Eligible patients. Patients with chronic or documented paroxysmal AF were eligible for the study. Patients at low risk according to Stroke Prevention in Atrial Fibrillation (SPAF) III stratification (7) or younger than 60 years of age
were not included. Eligible patients were divided in two groups: the high-risk group included nonvalvular plus prior embolism and patients with mitral stenosis with and without prior embolism. All others were included in the intermediate-risk group. Exclusion criteria were mechanical valve prosthesis, stroke in the previous six months, serum creatinine over 3 mg/dl, alcoholism or drug addiction, severe uncontrolled hypertension, diffuse arteriosclerosis, and indication for non-steroidal anti-inflammatory drugs or indication/contraindication for antiplatelet or anticoagulant therapy.

**Study design and organization.** The National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) is a prospective, multicenter, randomized open-label study. Thirteen Spanish hospitals participated according to the principles of the Helsinki Declaration. The ethical committee of each institution approved the protocol and the patient’s written informed consent was signed. Two blind events and safety committees, composed of members not involved in the running of the trial, validated all events and monitored the safety of treatments. The core center for data collection and statistical analysis was San Carlos University Hospital in Madrid. The Working Group on Thrombosis of the Spanish Cardiac Society had access to the database throughout the study.

The antiplatelet agent used was triflusal (Grupo Uriach, Spain), a drug structurally related to acetylsalicylic acid (11), of which clinical trials showed that 600 mg/day has similar biologic effects and clinical efficacy to aspirin 300 mg/day with fewer bleeding complications (12,13). The anticoagulant used was acenocoumarol (Novartis Farmaceutica, Spain), the coumarin derivative most used in several European countries.

Randomization was balanced, computer-generated, and administered centrally. It was also balanced by study center and by the three high-risk subgroups. The randomization sequence could not be previewed. Patients in the intermediate-risk group were randomized to one of the three arms: oral anticoagulation to a target INR of 2 to 3, triflusal 600 mg daily, or a combination of both with a target INR of 1.25 to 2. In the high-risk group, the triflusal-only arm was omitted and subjects were assigned to anticoagulation with a target INR of 2 to 3 or the combination therapy with a target INR of 1.4 to 2.4.

Demographic data, risk factors, concomitant heart disease, blood pressure, clinical examination, electrocardiogram, and echocardiogram were recorded at baseline. Clinical follow-up was scheduled every six months for a maximum of four years. In between, the patients were under the care of their general practitioners. Follow-up was interrupted after a primary outcome or a prosthetic valve implantation. Any possible way (hospital records, phone calls) was used to detect any new event in cases lost to follow-up. This information was registered in a final form. Anticoagulation was controlled at specialized units by recording mean treatment dose, mean INR, time within the preset range, number of INR controls out of the preset range, number of INR controls >3.5 and <2, and the intercontrol intervals.

**Outcome events.** Primary outcome was a composite of vascular death, transient ischemic attack (TIA), and nonfatal stroke or systemic embolism, whichever came first. We also prospectively registered as secondary events severe bleeding, MI, nonvascular death, and non-severe bleeding. These outcomes alone or in combination were also analyzed. The composite of primary outcomes and severe bleeding was jointly analyzed to evaluate the benefit-to-risk ratio.

Stroke and TIA were defined as focal neurologic deficits lasting >24 h or <24 h, respectively. Neuroimaging defined the ischemic or intracranial hemorrhagic etiology. Systemic embolism was diagnosed after an abrupt vascular insufficiency without previous clinical symptoms. Vascular death included either sudden or any other death occurring within 30 days after a vascular event or progressive heart failure. Bleeding was considered severe when requiring hospital admission, blood transfusion, or surgery (14).

**Statistics.** For sample size calculation in the intermediate-risk group, we used the aspirin and anticoagulation arms events rate of the SPAF II younger group (15) and Copenhagen Study on Atrial Fibrillation (AFASAK) I (3) trials. The composite of nonfatal stroke, TIA, systemic embolism, and vascular death in the aspirin arm was 4.72 per 100 person-years in the SPAF II study and 4.8 in the AFASAK I trial. The rates in the anticoagulation arm were 3.53 and 1.2, respectively. The anticoagulation arm event rate in the high-risk group was based on the European Atrial Fibrrillation Trial (EAFT) (16), where the primary event rate was 8.0. There were no published trials to assume event rate in the combined arms, because the anticoagulation intensity used resulted subtherapeutic, but Turpie et al. (17), using high anticoagulation intensity associated with aspirin 100 mg/day for embolic prevention in patients with prosthetic heart valves, showed a benefit of 61%. We hypothesized that, using a moderate level of anticoagulation in our combined arms, a 40% reduction in the event rate should be clinically relevant. Assuming these figures, in a four-year follow-up period, two-tailed alpha-error of 0.05, and a

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**Abbreviations and Acronyms**

AF = atrial fibrillation
AFASAK = Copenhagen Study on Atrial Fibrillation
CI = confidence interval
EAFT = European Atrial Fibrillation Trial
HR = hazard ratio
INR = international normalized ratio
MI = myocardial infarction
NASPEAF = National Study for Prevention of Embolism in Atrial Fibrillation
SPAF = Stroke Prevention in Atrial Fibrillation
TIA = transient ischemic attack
WARIS = Warfarin Aspirin Re-Infarction Study
power of 80%, the calculated cohort was 813 for each treatment arm of the intermediate- and 197 for the high-risk group.

The safety committee decided to review outcomes after the SPAF III study reported in September 1996 (7) the failure of the combined therapy arm. This therapy in our trial presented no greater number of events than the other arms, and the median INR in the combined arms of both intermediate- and high-risk groups was 1.93 and 2.08, respectively. A similar level of INR was maintained afterward. In February 2000, when the calculated sample for the high-risk group was complete, the events committee analyzed the outcomes, which were significantly lower in the combined arm. The committee then decided to also analyze the intermediate-risk group, and the combined therapy also showed a significant benefit compared with other arms. Therefore, it was decided to finish recruitment in this group and continue the follow-up for one more year of cases that had not completed the scheduled follow-up period.

Statistical analyses were performed according to the intention-to-treat and “on-treatment” principles. Baseline comparisons were performed using the chi-square test for categorical data and analysis of variance test for continuous data. A logistic multivariate analysis was made to adjust baseline comparisons. The incidences were expressed as rates (events per 100 person-years). We used the Kaplan-Meier method to calculate the four-year cumulative rate of outcome events until the first event occurred. The representation of these charts was cut at the median follow-up. We used the hazard ratio (HR), 95% confidence interval (CI) of a Cox regression model, and the log-rank statistics to express the efficacy and safety of the different treatments. All tests were carried out at a 0.05 level of significance. Statistical analysis was performed using SPSS (Version 8.0, SPSS Inc., Chicago, Illinois).

**RESULTS**

Recruitment started in June 1995 and stopped in February 2000. The study was closed in June 2001. The number of patients recruited was 1,209. Figure 1 shows their distribution: 714 entered the intermediate-risk group (median follow-up 965 days) and 495 entered the high-risk group (median follow-up 1,075 days). The following reasons for treatment withdrawals were registered: adverse events (9%), without significant difference among groups; and general practitioner’s or patient’s decision (9.3%). These withdrawals resulted in a change from the combined treatment to the anticoagulant alone in 56 patients. The treatment arms were balanced with respect to baseline characteristics (Table 1). Patients with prior embolism at baseline presented a significantly higher rate of female gender, hypertension, diabetes, ischemic heart disease, hyperlipidemia, and peripheral vascular disease; had a larger left atrium; and were older. However, multivariate analysis showed significant differences only for the last four of these factors.

Table 2 shows the anticoagulation control data. The combined therapy had a lower median INR than the corresponding anticoagulant arms (1.93 vs. 2.47 and 2.17 vs.

![Figure 1. Flow diagram of the NASPEAF. Lost to follow-up corresponds to those patients about whom no data about efficacy and safety is available. INR = international normalized ratio; ITT = intention to treat; IQR = interquartile range.](image-url)
Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th></th>
<th>Intermediate-Risk Group</th>
<th>High-Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Triflusal (n = 242)</td>
<td>Anticoagulant (n = 237)</td>
</tr>
<tr>
<td>Age, yrs (SD)</td>
<td>69.9 (8)</td>
<td>69.6 (7)</td>
</tr>
<tr>
<td>No risk factors, age 60–74 yrs</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Men</td>
<td>57.0</td>
<td>54.6</td>
</tr>
<tr>
<td>Current smokers</td>
<td>37.4</td>
<td>39.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.1</td>
<td>17.0</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>31.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Family history of thrombotic disease</td>
<td>20.4*</td>
<td>34.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42.7</td>
<td>45.0</td>
</tr>
<tr>
<td>Mean DBP, mm Hg (SD)</td>
<td>138 (17)</td>
<td>135 (18)</td>
</tr>
<tr>
<td>Mean SBP, mm Hg (SD)</td>
<td>80 (11)</td>
<td>79 (11)</td>
</tr>
<tr>
<td>NYHA functional class II to IV</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>Persistent/permanent atrial fibrillation</td>
<td>89.9</td>
<td>89.6</td>
</tr>
<tr>
<td>Bioprosthesis†</td>
<td>2.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Nonvalvular AF + prior embolism (n)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mitral stenosis + prior embolism (n)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mitral stenosis no prior embolism (n)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Data expressed in percentage, unless otherwise indicated. *p < 0.05 compared with the other two groups. †Bioprosthesis normal functioning are included in intermediate-risk group; if mitral valve area is narrower than 2 cm² they are included in the high-risk group.

DBP = diastolic blood pressure; LA = left atrium; LV = left ventricle; NYHA = New York Heart Association; SBP = systolic blood pressure.

2.50 in the intermediate- and high-risk groups, respectively. The combined arms also had a higher number of INR controls <2 in either risk group (67% vs. 21% and 39% vs. 18%) and a lower number of INR controls >3.5 (1.96% vs. 6.30% and 2.40% vs. 7.90%) (p < 0.001 for all).

Outcomes. Primary events in the intermediate-risk group were recorded in 42 cases (Table 3). Figure 2A shows the event-free survival curves and Figure 3 shows the HR. The combined therapy arm presented fewer primary events than the antiplatelet (HR 0.24 [95% CI 0.09 to 0.64]; p = 0.001) or the anticoagulant-alone group (HR 0.33 [95% CI 0.12 to 0.91]; p = 0.02). No significant difference in primary events was observed in the anticoagulant compared with the antiplatelet arm (HR 0.72 [95% CI 0.37 to 1.39]; p = 0.32). The combined therapy arm had a lower rate of embolism–TIA than the antiplatelet arm (HR 0.21 [95% CI 0.06 to 0.74]; p = 0.01) and lower vascular death rate than the anticoagulant arm (0.37 vs. 1.98, p = 0.01). It also showed a 61% relative reduction in outcome plus severe bleeding compared with either the antiplatelet (HR 0.39 [95% CI 0.17 to 0.87], p = 0.02) or the anticoagulant (HR 0.38 [95% CI 0.17 to 0.87]; p = 0.02) arms. The “on-treatment” primary outcome rates were 2.95, 2.34, and 0.55 in the anticoagulant, anticoagulant, and combined therapy arms, respectively, with a significant benefit in the combined therapy when compared with either the antiplatelet (p = 0.002) or the anticoagulant arms (p = 0.005).

There were 43 primary events in the high-risk group. Table 3 shows their distribution and Figures 2B and 3 show the primary event-free survival curves and the HR. The

Table 2. Anticoagulation Values in Different Therapeutic Groups

<table>
<thead>
<tr>
<th></th>
<th>Intermediate-Risk Group</th>
<th>High-Risk Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticoagulant</td>
<td>Combined</td>
</tr>
<tr>
<td>Number of INR controls</td>
<td>6,813</td>
<td>5,478</td>
</tr>
<tr>
<td>Preset INR range</td>
<td>2.00–3.00</td>
<td>1.25–2.00</td>
</tr>
<tr>
<td>Mean anticoagulant dose in mg (SD)</td>
<td>2.04 (0.80)</td>
<td>1.61 (0.70)*</td>
</tr>
<tr>
<td>Median INR</td>
<td>2.47</td>
<td>1.93*</td>
</tr>
<tr>
<td>(IQR: P25–P75)</td>
<td>(2.33–2.60)</td>
<td>(1.83–2.09)</td>
</tr>
<tr>
<td>Time within range, % (SD)</td>
<td>65 (22)</td>
<td>66 (25)</td>
</tr>
<tr>
<td>Time over range, % (SD)</td>
<td>16 (17)</td>
<td>31 (25)</td>
</tr>
<tr>
<td>Time below range, % (SD)</td>
<td>19 (18)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Mean inter-controls interval, days</td>
<td>26.50</td>
<td>27.20</td>
</tr>
<tr>
<td>Number INRs &lt;2, %</td>
<td>21</td>
<td>67*</td>
</tr>
<tr>
<td>Number INRs &gt;3.5, %</td>
<td>6.30</td>
<td>1.96*</td>
</tr>
</tbody>
</table>

*p < 0.001 compared with the anticoagulant arm.
INR = international normalized ratio.
The combined therapy, as compared with the anticoagulant therapy arm, decreased the aggregate embolism, stroke, and TIA rate by 56% in both the intermediate- and high-risk groups (Fig. 4A).

The combined therapy, as compared with the anticoagulant therapy, decreased the aggregate embolism, stroke, and TIA rate by 56% in both the intermediate- and high-risk groups (Fig. 4A).

Figure 4B shows the embolism-stroke-TIA event-free survival curves throughout anticoagulant therapy in the three subgroups of the high-risk group and in nonvalvular AF patients without prior embolism. The survival curves were similar in nonvalvular and valvular patients either with prior embolism at baseline (rates of 4.94 vs. 4.81, p = 0.98) or without embolism (1.43 vs. 1.26, p = 0.57). However, patients with mitral stenosis had a significantly lower incidence of several other risk factors: age (p < 0.001), diabetes (p = 0.04), hypertension (p < 0.01), and ischemic heart disease (p < 0.001). Patients with prior embolism had a significantly higher event rate than those without embolism at baseline (p < 0.006).

Adverse events. We recorded a total of 42 severe bleeding episodes (Table 3): the antiplatelet arm in the intermediate-risk group showed significantly fewer events than the anticoagulant and the combined therapy arms. No difference was found between the anticoagulant and the combined therapy arms. Fourteen bleeding events were intracranial (two in the antiplatelet arm, nine in the anticoagulant, and three in the combined arms). Fifteen hemorrhages were gastric, most of them in the combined therapy arms. By endoscopy, seven patients in the combined therapy group showed superficial mucosal erosions and three patients in the anticoagulant arm showed recent ulcers.

**DISCUSSION**

The NASPEAF allows us to present, for the first time, three new aspects of antithrombotic treatment in AF. These are the effect of anticoagulation alone versus combined therapy with moderate anticoagulation, the event rate in mitral stenosis versus nonvalvular patients, and the event rate in patients with prior embolism versus no embolism at baseline.

In the intermediate-risk group, primary outcome was lower with combined therapy than with the anticoagulant therapy despite the anticoagulant maintaining a lower me-
median INR and three times as many INR controls <2. Primary outcome plus severe bleeding was also lower with the combined therapy, making this therapy the more efficacious and safer treatment.

In the high-risk group, the combined therapy showed a significantly lower incidence of primary events when compared with the anticoagulant therapy. This benefit was obtained with a lower median INR than in the anticoagulant arm and with 39% of INR controls <2. Therefore, an INR of 2, considered by the EAFT (16) and Hylek et al. (18) as the lower limit of safety during anticoagulant therapy, is not applicable to patients receiving combined therapy.

We planned a primary outcome, similar to that of the EAFT (16), composed of vascular death, systemic embolism, and stroke. Primary outcome in other trials (7–9) was the composite of systemic embolism and stroke. When we analyzed this outcome in the NASPEAF, the combined
therapy compared with the anticoagulant therapy decreased the event rate of this aggregate by 56% in both the intermediate- and high-risk groups. Table 4 shows the characteristics and the embolism-stroke events rate in the anticoagulant-alone and the combined therapy arms in the NASPEAF and the three previous similar trials, but Edvardsson et al. (9) did not include an anticoagulation therapy arm. Our intermediate-group risk profile appears to be similar to that of the AFASAK II cohort (8) and our high-risk group appears to be similar to the SPAF III study (7). Although event rates with standard anticoagulation were similar, those with combined therapy in the intermediate- and high-risk groups in the NASPEAF showed significant benefit compared with the AFASAK II and SPAF III study, respectively. The possible explanation for this difference may be the higher anticoagulation intensity achieved in the NASPEAF (median INR 1.93 to 2.17 in the intermediate- and high-risk groups) compared with the other trials (median INR <1.3). The NASPEAF also showed that efficacious combined therapy needs a moderate anticoagulation intensity and that laboratory control is mandatory. Thus, INR levels <1.8 to 1.9 may not offer any significant benefit and levels >2.5 are not needed.

Patients with prior embolism, investigated in published trials, presented very high event rates with standard anticoagulation. The composite of embolism-stroke-TIA was 3.9 in the EAFT (16), 4.6 in the SPAF III study high risk (7), and 4.8 in the NASPEAF. The corresponding rates of vascular death were 4.1, 4.9, and 4.3 respectively, and severe bleeding was about 2 per 100 patients/year in the three trials. The NASPEAF showed that combined antiplatelet and moderate-intensity anticoagulation therapy could safely reduce the vascular event rate in this high-risk group of patients.

Our trial also investigated antithrombotic treatment in patients with AF plus mitral stenosis and in nonvalvular patients. The embolic event rate, during equal anticoagulant intensity, was similar in either the valvular or nonvalvular groups, without embolism (1.26 vs. 1.43) or with embolism at baseline (4.81 vs. 4.94). The existence of valve stenosis and a predominant female gender in patients with mitral stenosis were probably counterbalanced by an older age and a higher incidence of several other risk factors in nonvalvular patients. We have included mitral stenosis patients without prior embolism in the high-risk group, but these patients presented a lower event rate than we expected and should probably be included in the intermediate-risk group.

Patients assigned to antiplatelet therapy presented a relatively low event rate, consistent with other series of patients with relative low intrinsic risk (19).

In the WARIS II (10), anticoagulation or combined therapy were both superior to antiplatelet therapy alone in post-MI patients, but were not better or worse than each other. Here, combined therapy appeared to be superior to either anticoagulation or antiplatelet therapy alone in patients with AF; combined therapy could be indicated in patients with both pathologies.

Anticoagulant therapy was controlled at anticoagulation units. The percentage of INR tests within the preset ranges was 65 to 73, indicating a good control level (20). The median INR in the anticoagulant arms (target INR of 2 to 3) was 2.47 in the intermediate-risk group and 2.50 in the high-risk group. The preset range in the combined arm of

![Figure 3. Relative effect on vascular events of combined versus anticoagulant therapy. Log hazard ratio (HR) (95% confidence interval [CI]) = logarithm hazard ratio whose 95% CI (error bars) excludes the vertical line are statistically significant at the 5% level (or significant with p < 0.05). AMI = acute myocardial infarction.](image-url)
the intermediate-risk group was 1.25 to 2 and the median INR achieved was 1.93. The range in the combined arm of the high-risk group was 1.4 to 2.4 and the median achieved was 2.17; the achieved median INR in the combined arms was greater than planned because our hematologists did not want low anticoagulation intensity and tended to maintain the level of anticoagulation near the upper limit of the target.

Figure 4. Kaplan-Meier survival curves of the composite embolism-stroke-transient ischemic attack (TIA) in different groups of patients. (A) Survival curves in the combined therapy and anticoagulant arms of the intermediate- and high-risk groups. (B) Survival curves in groups of patients receiving anticoagulant therapy for INR (2 to 3). ACO = anticoagulant; Emb/embol = embolism; TIA = transient ischemic attack; other abbreviations as in Figure 2.
There was a tendency to preferential intracranial bleeding location with standard anticoagulation, consisting with a higher anticoagulation intensity (21). On the contrary, gastric bleeding was more common in the combined therapy arms. The acid component of trifusul could be responsible for the superficial erosions found by endoscopy, which lead to bleeding when a certain level of anticoagulation is added.

Different trials (17,22–25) investigated combined therapy in mechanic valve prosthetic patients. The incidence of severe bleeding seems to be dose-related to either antiplatelet or anticoagulant agent. Accordingly, there is a tendency to use a low antiplatelet dose in the combined therapy. The trifusul dose in our combined therapy arms was 600 mg/day, which corresponded to aspirin 300 mg/day, and the risk of nongastric severe bleeding was low. Two blind published trials, Trifusul in Myocardial Infarction (TIM) (12) in post-MI patients and Trifusul versus Aspirin in Cerebral Infarction Prevention (TACIP) (13) in post-cerebral infarction patients, compared trifusul 600 mg/day to aspirin 300 to 325 mg/day. In both studies, no difference in efficacy was found, but there was significantly higher major hemorrhage or central nervous system hemorrhage with aspirin. Also, in the WARIS II (10) the combination of aspirin 80 mg/day plus anticoagulation with an INR of 2.2 offered higher risk of bleeding than anticoagulation alone, for an INR of 2.8. Thus, although one can extrapolate from the NASPEAF that the combination of anticoagulation and aspirin is effective, a safe dose of aspirin cannot be determined, but the guidelines for valvular prosthesis (26) propose 75 to 100 mg/day in combined therapy.

The emerging benefit of direct antithrombin agents in patients with AF (27), similar to anticoagulation for INR of 2 to 3, may influence future antithrombotic therapy in these patients. However, an open question remains about the efficacy of antithrombin agents in patients with previous embolism and those with mechanical valvular prosthesis, in whom anticoagulation for an INR of 2 to 3 was not sufficiently effective. We probably need new trials to evaluate the combination of antiplatelet and direct antithrombin agents in these patients.

In conclusion, the addition of antiplatelet therapy to reduced-intensity anticoagulation in AF patients stratified for risk of stroke significantly reduces subsequent events compared with patients receiving standard anticoagulation, and does so without increasing bleeding risk.

Acknowledgment
We are grateful to Dr. Daniel Singer (Massachusetts General Hospital) for helpful comments on early drafts of the manuscript.

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REFERENCES


APPENDIX

For a list of the Events Committee, Safety Committee and Data Monitoring, Central Coordination and Data Management, Statistical Analysis, and Centers and Principal Investigators, please see the October 19, 2004, issue of JACC at www.onlinejacc.org.