

## **Triflusal in atrial fibrillation**

The recently published National Study for Prevention of Embolism in Atrial Fibrillation (NASPEAF) study <sup>1</sup> is a prospective, multicenter, randomized open-label clinical trial, comparing the efficacy and tolerability of triflusal plus moderate intensity oral anticoagulation versus standard oral anticoagulation in patients with atrial fibrillation (AF).

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 <sup>2</sup> or < 60 years of age were not included. Eligible patients were divided in two groups: the high-risk group included patients with nonvalvular AF but 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 >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.

Randomization was balanced, computer-generated, and administered centrally. Patients in the intermediate-risk group were randomized to one of three arms: oral anticoagulation with acenocoumarol (a vitamin K antagonist commonly used in Europe) 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 of 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 present range, number of INR controls  $> 3.5$  and  $< 2$ , and the intercontrol intervals.

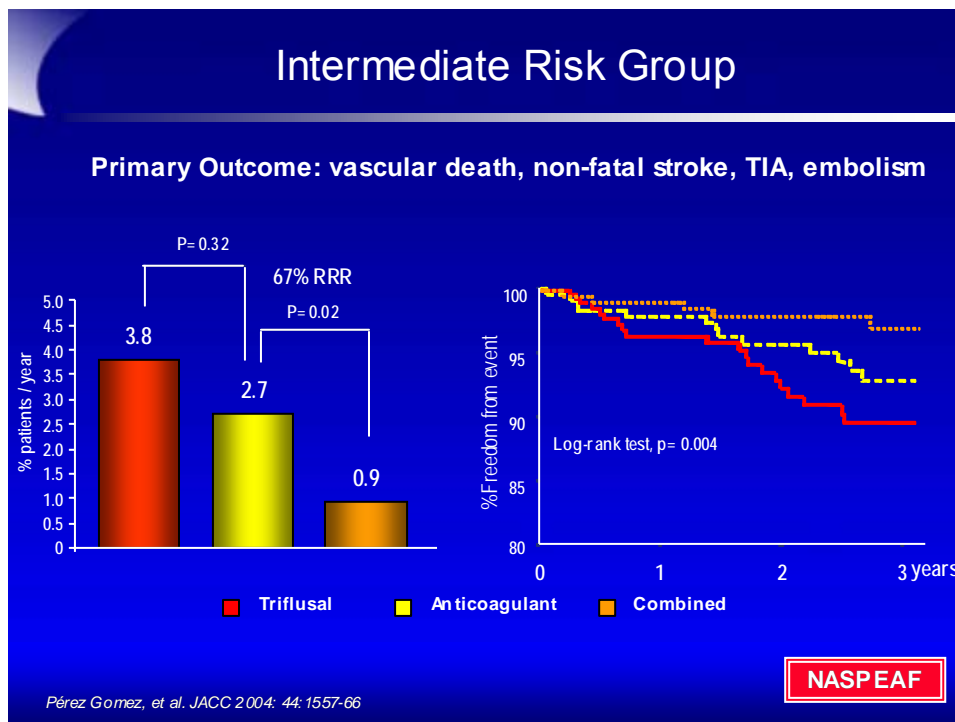
Primary outcome was a composite of vascular death, TIA and nonfatal stroke or systemic embolism, whichever occurred first. Secondary events were severe bleeding, AMI, nonvascular death, and non-severe bleeding. These outcome events were analyzed alone or in combination. The composite of primary outcome events 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 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.

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 has access to the database throughout the study.

One thousand two hundred nine patients were included and 1159 patients were evaluable for efficacy. After a median follow-up of 2.76 years, primary outcome was lower in the combined therapy than in the anticoagulant arm in both the intermediate ([HR: 0.33; 95% CI: 0.12-0.91;  $p = 0.02$ ) and the high-risk group (HR: 0.51; 95% CI: 0.27-0.96;  $p = 0.03$ ).

In the intermediate-risk group, primary outcome was lower in the combined therapy than in the antiplatelet group (HR: 0.24; 95% CI: 0.09-0.64;  $p = 0.001$ ) and the combined therapy arm had a lower rate of embolism-stroke TIA than the antiplatelet arm (HR: 0.21; 95% CI: 0.06-0.74;  $p = 0.01$ ) and a lower vascular death rate (expressed as rate per 100 person-years) than the anticoagulant arm (0.37 versus 1.98,  $p = 0.01$ ). It also showed a 61% relative reduction in primary end-points plus severe bleeding compared with either the antiplatelet (HR: 0.39; 95% CI: 0.17-0.87;  $p = 0.02$ ) or the anticoagulant (HR: 0.38; 95% CI: 0.17-0.87;  $p = 0.02$ ) arms. In the high risk group the combined therapy arm had a lower vascular death (expressed as rate per 100 person-years) than the anticoagulant arm (1.05 versus 2.79;  $p < 0.05$ ).



**Fig. 1**

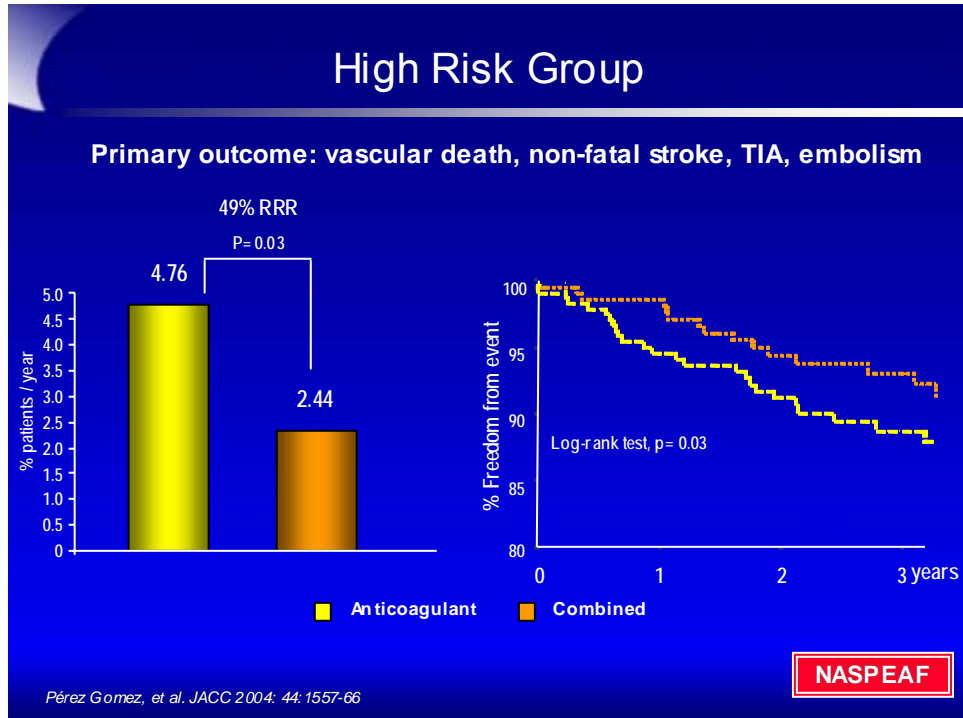
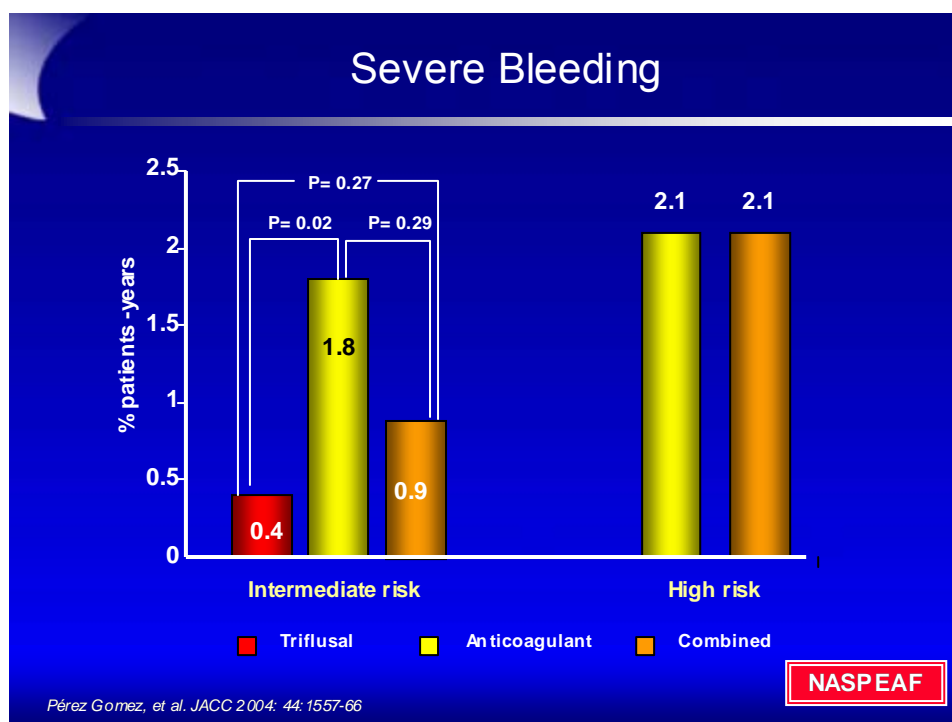


Fig. 2

No differences concerning severe bleeding were observed between arms either in the intermediate or in the severe-risk groups.



**Fig. 3**

Of interest is that the combined therapy had a lower median INR than the corresponding anticoagulant arms (1.93 vs 2.47 and 2.17 vs 2.50 in the intermediate and high risk groups, respectively;  $p < 0.001$  for combined versus anticoagulant arm in both intermediate and high risk groups).

In a subanalysis<sup>3</sup> of the NASPEAF study<sup>1</sup>, the authors found that in mitral stenosis patients combined therapy reduced the risk of vascular events by 58.3% compared with anticoagulant alone therapy. Another subanalysis<sup>4</sup> of the same study<sup>1</sup> showed that in patients aged  $\geq 75$  years combined therapy reduced cardiovascular events in comparison with standard anticoagulant therapy (HR: 0.33; 95% CI: 0.13-0.83;  $p = 0.012$ ). The incidence of serious bleeding was lower with the combined treatment but did not achieve statistical significance.

NASPEAF study <sup>1</sup> demonstrated for the first time that the addition of antiplatelet therapy (triflusal) with the aim of reducing the intensity of anticoagulation in AF patients stratified according to risk of thromboembolism, significantly decreases subsequent vascular events compared with patients receiving standard anticoagulation, and does so without increasing bleeding risks. This differs from findings in other studies combining low-dose warfarin and aspirin <sup>2,5,6</sup>. The importance of the NASPEAF study <sup>1</sup> has been emphasized in the last NICE Guideline for management of AF <sup>7</sup> published by the Royal College of Physicians of London in 2006. The Guideline confers a level of evidence 1+ to the results of the NASPEAF study <sup>1</sup>.

## **References**

- 1.- Pérez-Gómez F, Alegría E, Berjón J, et al. , for the NASPEAF Investigators. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation. *J Am Coll Cardiol* 2004; 44: 1557-66.
  
- 2.- Stroke Prevention in Atrial Fibrillation III Investigators. Adjusted dose warfarin versus low-intensity, fixed dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial. *Lancet* 1996; 348: 633-8.
  
- 3.- Pérez-Gómez F, Salvador A, Zumalde J. Effect of antithrombotic therapy in patients with mitral stenosis and atrial fibrillation: a sub-analysis of NASPEAF randomized trial. *European Heart Journal* 2006; 27: 960-7.
  
- 4.- Pérez-Gómez F, Iriarte J A, Sumalde J, et al. Antithrombotic therapy in elderly patients with atrial fibrillation: effects and bleeding complications: a stratified analysis of the NASPEAF randomized trial. *Eur Heart J* 2007; 28: 996-1003.
  
- 5.-Gullov A L, Koefoed B G, Petersen P, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin and Anticoagulation Study. *Arch Intern Med* 1998; 158: 1513-21.
  
- 6.-Edvarson N, Juul-Moller S, Omblus R, Pehersson K. Effect of low dose warfarin and aspirin on stroke versus no treatment on stroke in a medium-risk patient population with atrial fibrillation. *J Intern Med* 2003; 254: 95-101.

7.- Atrial Fibrillation. Royal College of Physicians of London National clinical guideline for management in primary and secondary care. <http://www.nice.org.uk/nicemedia/pdf/cg036fullguideline.pdf> 2006. Consulted on 16 November 2007.

## Figures legends

### Fig 1

In the intermediate-risk group, the incidence of the primary outcome in the intent-to-treat analysis was significantly lower with combination therapy (0.9%) than triflusal (3.8%) or acenocoumarol (2.7%) monotherapies. The difference between the two monotherapies was not statistically significant. Combination therapy versus the other treatment schedules also produced significantly lower rates of the primary outcome.

### Fig 2

For patients in the high-risk group, triflusal plus acenocoumarol versus acenocoumarol monotherapy was associated with significantly lower rates of the primary endpoint and vascular death.

### Fig 3

The NASPEAF study of thromboprophylaxis in atrial fibrillation documented a significantly lower risk of severe bleeding in triflusal-treated patients in the intermediate-risk group than in patients treated with acenocoumarol, or triflusal plus acenocoumarol (0.4% vs 1.8% vs 0.9%;  $p < 0.05$ ). There was no difference in severe bleeding episodes in the high risk group.