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BRIEF COMMUNICATION

Levels of PAI-1 and outcome after electrical cardioversion for atrial fibrillation

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Atrial fibrillation (AF) is associated with a prothrombotic state and increased risk of stroke [1,2]. However, the relation between AF and fibrinolytic activity is presently unclear. Elevated levels of both tissue plasminogen activator (tPA) and plasminogen activator inhibitor type 1 (PAI-1) have been found in patients with AF [3–5], thus the net effect on fibrinolysis may be conjectural.

Treatment with angiotensin II type 1 receptor blockers (ARBs) has been shown to reduce the incidence of new-onset AF as well as cardiovascular events in hypertensive patients and patients with heart failure [6–8]. The mechanisms behind these effects are poorly understood. Angiotensin II has been shown to influence the fibrinolytic system by inducing PAI-1 in the vasculature and increasing circulating levels of PAI-1 [9,10], however studies on the effect of treatment with ARBs on the fibrinolytic system have yielded conflicting results [11–15].

The present study is a prespecified subset analysis of the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study [16]. We reported earlier that high levels of high sensitivity C-reactive protein (hs-CRP) were associated with increased risk of AF recurrence after electrical cardioversion in the CAPRAF study. Neither sustained sinus rhythm for 6 months nor treatment with candesartan influenced the levels of hs-CRP [17].

We hypothesized that 1) the levels of tPA antigen or PAI-1 activity measured before electrical cardioversion for persistent AF would predict rhythm outcome after cardioversion; 2) maintenance of sinus rhythm for 6 months would influence these parameters; and 3) treatment with candesartan would improve fibrinolytic activity. Levels of von Willebrand factor (vWf) and hs-CRP, as markers of endothelial dysfunction and inflammation respectively, were included for comparison.

Materials and methods

Briefly, in the CAPRAF study, 171 patients undergoing planned electrical cardioversion for persistent AF were randomised to receive candesartan 8 mg once daily (n=86) or matching placebo (n=85) for 3–6 weeks before and candesartan 16 mg once daily or placebo

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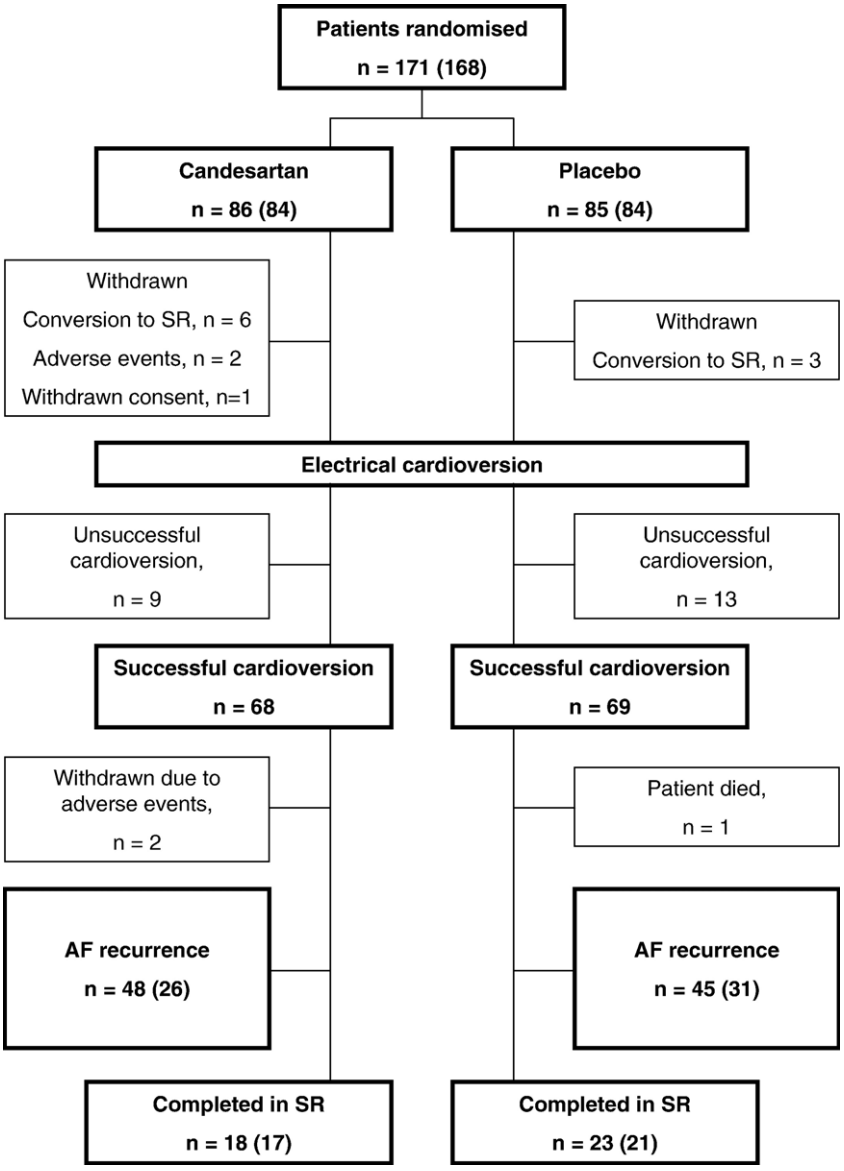

Figure 1 Flow chart of the Candesartan in the Prevention of Relapsing Atrial Fibrillation (CAPRAF) study. *n* = number of patients. The numbers in parenthesis represent the number of patients at each stage from which blood samples were available.

for 6 months after cardioversion (Fig. 1). Blood samples were available at baseline for 168 patients and at the end of the study for 95 patients (Fig. 1). Patients in whom AF recurred during 6 months follow-up had their final blood sample drawn at that time.

Venous fasting blood samples were drawn between 8 and 9 a.m. Citrated blood (Becton Dickinson Vacutainer tubes containing 0.129 mol/L trisodium citrate in dilution 1:10) was collected and placed on ice until platelet poor plasma was obtained by centrifugation at 4 °C and 2500 ×*g* for 20 min. The plasma samples were kept frozen at −70 °C until they were analysed in batch for determination of tPA antigen, PAI-1 activity and vWf. Commercially available assays were used. Measurement of tPA antigen was performed with TintElize tPA (coefficient of variation = 3.5%), PAI-1 activity was determined by Spectrolyse/pL (coefficient of variation = 4.4%), both Biopool AB, Umeå, Sweden. vWf was measured by Asserachrom vWf Stago Diagnostica, Asnieres, France (coefficient of variation = 8%). Hs-CRP was measured in serum by a commercially available ELISA method (DRG Diagnostics, DRG Instruments GmbH, Germany, coefficient of variation <5%) [17].

Statistical methods

Data are presented as mean ± standard deviation for normally distributed continuous variables, while continuous variables not normally distributed are expressed as median and interquartile range. Categorical variables are shown as frequencies (%).