

Antithrombotic Therapy in Native Heart Valve Disease

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In establishing the indication for anticoagulation of patients with native heart valve disease, those with thromboembolic events and/or atrial fibrillation (AF) must be distinguished from patients with sinus rhythm. Anticoagulation should be started as a matter of principle in patients with thromboembolic events and/or AF who do not undergo valve replacement. However, a more differentiated procedure is mandatory for patients with sinus rhythm. If the left atrium is enlarged, spontaneous echo contrast is detected, and/or there is no atrial contraction and/or reduced left ventricular pump function (e.g., in patients with mitral valve stenosis), then anticoagulation with a target INR of 2.5 is indicated, even in those with sinus rhythm. Whereas rheumatic mitral valve stenosis predominates in developing countries, aortic stenosis (AS) predominates in developing

The prevalence of heart valve disease differs significantly among various regions of the world. One major reason is the difference in the incidence of rheumatic fever and consequent 'rheumatic' valve lesions, as well as differences in life expectancy. In industrialized countries with their aging populations, the incidence of degenerative (mitral regurgitation and calcific aortic stenosis) valve lesions is increasing (1). Within an aging population, arteriosclerosis of the aorta is progressing, and must be considered a potential source of embolic events (2). Patent foramen ovale (PFO) and/or atrial septal aneurysm (ASA) are considered to be risk factors for the manifestation of ischemic stroke (3).

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countries. These AS patients mainly suffer microemboli that often determine the prognosis in patients with calcification of the mitral annulus. Anticoagulation is not recommended in calcific microemboli. If there are simultaneous atherothrombotic plaques of the aortic arch >5 mm in size owing to an often more complex cardiovascular risk profile, then warfarin treatment is indicated. Mitral valve prolapse (MVP), patent foramen ovale and atrial septal aneurysm are potential sources of embolism that may cause stroke. On their own, these congenital lesions do not entail an indication for anticoagulation. This applies in particular to patients with MVP in whom secondary prevention of stroke can be attained with 100 mg aspirin.

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Aortic valve disease

Patients with aortic stenosis (AS) usually experience a long asymptomatic period (4). However, following the onset of symptoms, the prognosis is poor and the optimal time frame for surgical intervention is often missed (5,6). Symptomatic patients with aortic regurgitation (AR) also have a poor prognosis unless timely surgery is carried out (7). The risk for thromboembolic events in chronic aortic valve disease is much lower than for mitral valve disease, and is clearly dependent on procoagulative confounders such as atrial fibrillation (AF), left atrial (LA) size and mitral annular calcification (6,7). Di Tullio et al. analyzed risk factors for embolic events in 350 patients aged over 40 years who suffered a first ever ischemic stroke (9). Even after adjustment for other risk factors, patients with a LA index (LA diameter divided by body surface area) >25 mm/m² had a two-fold higher risk of stroke than patients with a normal LA size. Few data exist on the benefit of anticoagulation in patients with left ventricular dysfunction, but the SAVE investigators reported a two-fold increase in stroke risk for patients with a left

ventricular ejection fraction (LVEF) <30% as compared to those with a LVEF >35% (10).

Atherosclerosis of the aorta and mitral annular calcification

Atherosclerosis of the aorta may be a source for aorto-arterial embolism. Aortic atheromas are best graded according to echocardiographic findings as grades I to V. A grade IV atheroma is one which protrudes ≥ 5 mm into the aortic lumen, while grade V indicates a protrusion which is more or less mobile, regardless of size (11). Grade IV and V atheromas are associated with a high incidence of embolic events (12). Consequently, oral anticoagulation with a target international normalized ratio (INR) of 2.5 is recommended (Table I).

Mitral annular calcification is associated with concomitant heart disease, established cardiovascular risk factors, and increasing age. Among 1,159 patients enrolled in the Framingham study, echocardiography revealed mitral annular calcification in 10% of consecutive males and in 15% of consecutive female subjects (14). During nine years of follow up, there was a significantly higher incidence of stroke in patients with, rather than without, mitral annular calcification, especially if patients also suffered from AF. Mitral annular calcification is therefore a strong predictor for stroke, especially if AF is also present. Consequently, long-term oral anticoagulation with a target INR of 2.5 is recommended (13).

Mitral stenosis

Mitral stenosis is associated with the highest incidence of thromboembolic complications of all non-inflammatory valve lesions (8,15,16). Thrombi may be localized with almost equal frequency either in the LA appendage or on the LA wall. In the Framingham study, the presence of AF was seen to increase the risk for thromboembolism between three- and 18-fold. The frequency of thromboembolic events is significantly increased with the progression of mitral valve obstruction and the presence of AF (16). Among non-anticoagulated patient with mitral stenosis, embolic events are recurrent in 30-65% of cases, and 60-65% of these events occur within one year after the index event (17). A five-fold higher thromboembolic hazard has been documented for patients with mitral stenosis, who presented with permanent spontaneous echo contrast (odds ratio (OR) 5.2) during a mean follow up period of more than nine years (17). The embolic hazard was more than two-fold higher in patients with no active atrial contraction compared to those with a normal LA function (OR 2.3) or in patients with a LA index >31 mm/m² (OR 1.98) (17). Intermittent AF was also accompanied by an increased risk for embolic episodes (OR 1.57).

Prothrombin fragments I and II have been taken as indicators of an increased regional coagulation activity in mitral stenosis patients. No differences in prothrombin fragments I and II concentrations in the femoral vein and the left atrium have been found in mitral stenosis patients without LA spontaneous echo contrast, while patients presenting with spontaneous echo contrast had higher concentrations of prothrombin

Table I: Recommendations of the sixth ACCP Consensus Conference of antithrombotic therapy in heart valve disease (13).

Type of disease	Comorbidity	INR	Aspirin	Grade
Rheumatic mitral stenosis	Previous embolism, AF	2.5	-	1 C
	SR+LA >55 mm and/or SEC	2.5	-	2 C
	Recurrent embolism	3.0	100 mg	1 C
MAC and/or MR MVP	Systemic embolism/AF	2.5	-	2 C
	-	-	-	1 C
	Unexplained TIA	-	100 mg	2 C
	Recurrent TIA/stroke, AF	2.5	-	1 A
Aortic valve	-	-	-	2 C
Aortic arch	Plaque >4 mm, mobile atheroma	2.5	-	2 C
PFO/ASA	Unexplained TIA and demonstrable venous thrombosis, pulmonary embolism	2.5	-	1 C

AF: Atrial fibrillation; ASA: Atrial septal aneurysm; LA: Left atrial size; MAC: Mitral annular calcification; MR: Mitral regurgitation; MVP: Mitral valve prolapse; PFO: Patent foramen ovale; SEC: Spontaneous echo contrast; SR: Sinus rhythm; TIA: Transient ischemic attack.

fragments in the left atrium than in the femoral veins, regardless of the rhythm (sinus rhythm versus AF). Higher regional clotting factor activity as demonstrated by spontaneous echo contrast is beneficially influenced by oral anticoagulation therapy (15).

Mitral valve prolapse

Mitral valve prolapse (MVP) has for many years been considered a risk factor for stroke and other embolic events. Gilon et al., who compared 130 consecutive patients below 55 years of age with ischemic stroke in a case-control study including 263 controls, did not find any correlation between MVP and the incidence of stroke (20). The incidence of MVP was 1.9% in all patients (OR 0.7; CI 9.15-2.80), 2.8% in those with unexplained stroke (OR 1.06; CI 0.11-5.73), and 2.7% in controls. Differences in the published incidences of 'stroke' in patients with MVP may be entirely due to the definition of stroke. There is evidence that transitory ischemic attacks are frequently found in patients with mitral prolapse syndrome (21), but they are likely to be the consequences of small platelet aggregates due to abnormal platelet function in MVP patients (22).

Patent foramen ovale/atrial septal aneurysm

Patent foramen ovale without ASA has been linked with an increased risk for stroke. In a study by Mas et al. which included 532 patients (aged 18-55 years) with stroke of unknown origin, recurrent strokes during a follow up period of approximately four years occurred in 4.2% of all patients (95% CI 1.8-6.6%) (23). The stroke recurrence rate was 2.3% in patients with a PFO (95% CI 0.3-4.3%), but 15.2% (95% CI 1.8-28.6%) and a concomitant ASA. No significant differences in recurrence rate for stroke were found in patients with or without PFO if they were receiving either warfarin or aspirin. In patients with cryptogenic stroke, oral anticoagulation reduced the risk for recurrent events by 50%, irrespective of an existing PFO (OR 0.52; CI 0.16-1.67 versus OR 0.50; CI 0.19-1.31 without PFO). Anticoagulation (target INR 2.5) in combination with aspirin is therefore recommended after a first episode of unexplained cryptogenic stroke, or in patients with PFO plus demonstrable venous thrombosis or pulmonary embolism.

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