

Prophylaxis of Thromboembolic Events in Patients With Atrial Fibrillation After Coronary Stent Implantation, A Retrospective Analysis of 30-days Bleeding and Embolic Events

¹Axel Schlitt, ¹Gunnar H. Heine, ²Sabine Heine, ¹Bernhard Schwaab and ³Armin Heisel
Departments of Medicine III and Medicine IV, University of the Saarland, Homburg/Saar, Germany
¹Department of Medicine III, Martin Luther-University, Halle, Germany
²Department of Pediatrics, University of the Saarland, Homburg/Saar, Germany

Abstract: Prophylactic oral anticoagulation is indicated in patients with Atrial Fibrillation (AF) and high risk for thromboembolic events. The anticoagulant regimen is not standardized for patients with AF after coronary stenting, which requires dual antiplatelet therapy comprising aspirin and ADP –antagonists for at least four weeks. Low Molecular Weight Heparin (LMWH) is widely used in these patients. We retrospectively compared two groups of patients with permanent AF who underwent coronary stent implantation. 47 patients in group I received 320 mg aspirin Once Daily (OD) and 250 mg ticlopidine twice daily (BID) for four weeks without additional anticoagulation. In group II 11 patients received 320 mg aspirin OD, 250 mg ticlopidine BID and additionally subcutaneously administered LMWH in a therapeutic dosage. Within four weeks after coronary intervention, 5 vascular or bleeding complications occurred in group I (8%) and 4 in group II (36%) ($p=0.035$ by Fisher's exact test). One embolic event was observed in group I, whereas no embolic event occurred in group II ($p=0.08$). The results of our study suggest that the combination of dual antiplatelet therapy in addition to anticoagulation with LMWH may significantly raise the risk of vascular and bleeding events in patients with AF after coronary stent implantation. However, as we observed one embolic event in the patients without additional anticoagulation, data from a prospective randomized trial are needed in order to clarify the optimal therapeutic approach to patients with AF undergoing coronary stent implantation.

Key words: Atrial fibrillation, coronary heart disease, anticoagulation, coronary stent implantation

INTRODUCTION

Atrial Fibrillation (AF) frequently occurs in patients with Coronary Heart Disease (CHD)^[1]. Thus, a large number of patients undergoing coronary interventions suffer from AF. Several clinical trials have shown that combined antiplatelet therapy comprising aspirin and an ADP –antagonist (ticlopidine, clopidogrel) given for a minimum of four weeks is the most effective pharmacologic approach to prevent subacute stent-thrombosis after coronary stent implantation^[2-4].

Oral anticoagulation is recommended in patients with AF and high risk for thromboembolic events due to its superiority to aspirin^[5]. In patients undergoing medical interventions, oral anticoagulation may periprocedurally be replaced by the subcutaneous administration of low molecular heparin (LMWH) with adequate safety and efficacy^[6]. There is no standard regimen for the prevention of thromboembolic events in patients suffering from AF after coronary stent implantation. The combination of aspirin and an ADP–antagonist, which prevent subacute stent thrombosis, with subcutaneously administered

LMWH, which may reduce the incidence of embolic events, is widely used in these patients. However, the potentially increased risk of bleeding and vascular complications has not been thoroughly assessed.

MATERIALS AND METHODS

We retrospectively investigated the incidence of embolic, vascular and major bleeding complications in patients with AF, within 30 days after coronary stent implantation. We included patients with permanent AF who underwent elective heart catheter procedure in our institution because of stable angina pectoris between January 1998 and March 1999.

Two groups of patients were compared: 47 patients received a combined antiplatelet therapy comprising 320 mg of aspirin Once daily (OD) and 250 mg ticlopidine twice daily (BID), without additional LMWH –therapy (group I).

11 patients received 320 mg of aspirin OD, 250 mg ticlopidin BID and additionally subcutaneously

administrated LMWH (5,700 IU nadroparin BID [n=2] or 5,000 IU dalteparin OD [n=9]).

No patient received oral anticoagulation or unfractionated heparin after hospital discharge during the 30 days study period.

Major bleeding was defined as any cerebral hemorrhage or bleeding of any other site which required red cell transfusions; vascular events were defined as aneurysms of the femoral artery or arteriovenous fistula. Embolic events comprised embolic stroke and embolism in visceral and peripheral arteries.

The incidence of major bleeding episodes, of vascular events and of embolic events was compared between the two groups by Fisher's exact test.

RESULTS AND DISCUSSION

The two groups did not differ in sex distribution and age (Table 1). No patient died within the four week study period.

In group 1 major bleeding requiring blood transfusion and vascular complications occurred in four patients (see table 1), three of whom had an aneurysm of the femoral artery, one patient had an extended groin hematoma. In two of three patients with aneurysms surgical repair was necessary. One patient suffered from an embolic event of the lower limb, which was successfully treated with prolonged intravenous administration of unfractionated heparin without need for surgical intervention or lysing therapy.

In group 2 major bleeding complications and vascular complications occurred also in four patients: one patient had an aneurysm of the femoral artery, which required blood transfusion and surgical repair, two patients received blood transfusion for gastroscopically proven gastric bleeding and one patient developed an extended haemorrhage of the soft tissue of the abdominal wall at the site of LMWH-injections, requiring blood transfusions. Embolic events were not observed in group 2.

Vascular and major bleeding complications were significantly more often found in group 2 (8% versus 36%, p=0.035). The incidence of embolic events did not differ significantly between the two groups (2% versus 0%, p=0.08).

Our study suggests that the administration of LMWH in addition to dual antiplatelet therapy with ADP-antagonists and aspirin significantly increases the risk of bleeding complications in patients with AF after coronary stent implantation. However, the combination of ADP-antagonists with aspirin without addition of LMWH was

Table 1: Comparison of group 1 (325 mg aspirin OD, 250 mg ticlopidine BID) and group 2 (325 mg aspirin OD, 250 mg ticlopidine BID, LMWH)

	Group 1	Group 2
n	47	11
male	72.3 %	72.7 %
mean age, years ± SD*	68.8±6.9	69.2±6.7
bleeding and vascular complications	4 (8%)	4 (36%)
aneurysms of the femoral artery	3	1
extended groin hematoma‡	1	0
gastrointestinal bleeding#	0	2
other bleeding complications§	0	1
embolic events	1 (2%)	0

* standard deviation; ‡ >5cm diameter; # gastric bleeding; § extended soft tissue hemorrhage of the abdominal wall and occlusion of a lower limb artery

not sufficient to prevent thromboembolic complications in all patients with AF in our study. Unfortunately, our results underline the uncertainty regarding the treatment of patients with AF under combined antiplatelet therapy. Although LMWH and the combination of ADP-antagonists and aspirin are widely used, data from other trials can also not clarify, which treatment is safe and effective in this subgroup of patients after coronary stent implantation.

One small nonblinded control study in patients with chronic AF showed that monotherapy with 7,500 IU nadroparin reduces the incidence of arterial embolism by one third^[7]. In the ACE-trial, enoxaparin treatment was not inferior to a standard anticoagulation with UFH and oral anticoagulation in patients after cardioversion of non-valvular AF^[8]. Thus, the administration of LMWH seems to protect from embolic complications in patients with AF.

The data for the efficacy of ADP-antagonists and aspirin in patients with chronic AF are limited. Two small studies reported a reduction in markers of thrombosis in patients with standard anticoagulation with cumarins, but not in patients taking aspirin and clopidogrel^[9,10]. This suggests that the combination of clopidogrel and aspirin is not effective in the prevention of thromboembolic events in patients with chronic AF, which is in agreement with the episode of an embolic event in a patient with AF and no therapy with LMWH reported by us.

Regarding the combination of LMWH with ADP-antagonists and aspirin in patients receiving oral anticoagulation, to our knowledge only one trial was published. McDonald et al. reported a 4.2% incidence of severe vascular or bleeding complications and no embolic events in 119 patients under combined therapy of clopidogrel, aspirin and enoxaparin during a one month study period after cardiac catheterization^[11].

Only prospective studies can clarify whether the administration of LMWH in conjunction with aspirin and ADP-antagonists might be beneficial for patients with AF after coronary stent implantation.

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