The Impact of Concomitant Use of Statins and Vitamin K Antagonist on Bleeding Complications in Patients with Non-valvular Atrial Fibrillation

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**Background:** Statins have been shown to have protective effect against both venous and arterial thrombosis by coagulation cascade interference. However, whether this anticoagulation effect could result in an increased risk of bleeding when concomitant used with vitamin K antagonist (VKA) remains unclear considering the potential interaction between these two agents.

**Objective:** The aim of this study was to evaluate the influence of statins on the bleeding risk in non-valvular atrial fibrillation (AF) patients taking VKA.

**Methods:** Data of patients with non-valvular AF, aged 18 years or older and consecutively treated with VKA between January 2013 and December 2015, were identified through Thammasat University Hospital database. Patients were stratified into two groups based on statin use. Total and major bleeding events, defined by the ISTH criteria, of both groups were compared. High potency statins was defined as atorvastatin 40-80 mg/d or rosuvastatin 20-40 mg/d.

**Results:** The analysis included 503 AF patients (289 statin users and 214 non-statin users) with a median age of 71 years. Among 289 statin users, 181 patients used high-potency statins. Demographics were not different between the two groups, except statin users had higher CHA2DS2-VAS (median of 3 vs 2, P<0.0001) and used more antiplatelets (6.9% vs 0.5%, P<0.0001). The median time in therapeutic range of VKA was 66.7% in the statin user group and 69% in the non-statin user group (P = 0.49), while median time of VKA exposure was 40 vs 35 months, respectively (P = 0.06). The incidence of total bleeding events was not significantly different between both groups, with a 3-year cumulative incidence of 11.2% in statin users and 8% in non-statin users (P = 0.16). However, statin use was associated with higher incidence of major bleeding compared with non-statin users (6% vs 1.6% cumulative incidence at 3 years, P = 0.012) despite a comparable median INR at the time of bleeding (4 in both groups, P = 0.69). The highest incidence of major bleeding was seen in high-potency statin users (7.1% at 3 years, Figure 1). High potency statin use (HR 2.61, 95%CI 1.13–6.02, P = 0.02) and CHA2DS2-VAS > 2 (HR 3.86, 95%CI 1.23–12.11, P = 0.02) independently predicted risk of major bleeding in multivariable analysis.

**Conclusion:** The concomitant use of high potency statins and VKA increases a risk of major bleeding in patients with non-valvular AF regardless of INR. Further studies are needed to determine potential effects of statins on coagulation mechanism.

**Keywords:** Atrial fibrillation, Vitamin K antagonist, Statin
Figure 1. Cumulative incidence of major bleeding between statin users vs. non-statin users.