Trial design, statins, atrial fibrillation, and prevention: Four horsemen of the apocalypse

To the Editor,

We have read with great interest the article entitled "Efficiency of postoperative statin treatment for preventing new onset postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting: a prospective randomized study" published in the June 2014 issue of The Anatolian Journal of Cardiology by Aydın et al. (1). This article was about the effect of postoperative statin treatment on new onset postoperative atrial fibrillation (POAF) in patients undergoing isolated coronary artery bypass grafting (CABG). The study consisted of 60 consecutive patients who were divided into two groups: those undergoing postoperative statin treatment (n=30) and those not undergoing it (n=30). They concluded that atorvastatin treatment (40 mg), when started in the early postoperative period after isolated CABG, reduces the incidence of new-onset POAF.

AF is the most common cardiac arrhythmia after cardiac surgery, which generally occurs in 20%-40% of patients (2). POAF may be multifactorial and involves an interaction between surgical trauma, preexisting atrial pathology, activation of the inflammatory response and increased adrenergic tone (3).

POAF generally occurs between days 2 and 4 after surgery, with a peak incidence on the second day (3). Several randomized controlled trials support the use of longer duration statin therapy preoperatively to reduce the incidence and risk of developing AF after elective cardiac surgery (4). In contrast, the authors of the present study (1) preferred to start atorvastatin treatment in the early postoperative period (average of 6 h after the operation). Inflammation has a major role in the pathogenesis of POAF, and the occurrence of anti-inflammatory effects of statins requires approximately 30 days after their initiation (5). In the present study (1), the time between surgery and AF development is similar in both groups. Therefore, a major point of discussion is after how many days or hours after should postoperative statin therapy be started or should be expected to obtain the beneficial effects of statins in a relatively short time interval. More importantly, most patients are often unable to take oral medications shortly after surgery, and there is no intravenous formula for statins.

In cardiac surgery, manipulation of the pericardium is strongly associated with the development of POAF. Hence, it would be very useful if Aydın et al. (1) information about the occurrence of acute postoperative pericarditis and the development of AF in both groups.

In conclusion, larger randomized studies are required to confirm the possible beneficial effects of statins on AF when administrated postoperatively.

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Author`s Reply

To the Editor,

We thank the authors for their comments on our article entitled "Efficiency of postoperative statin treatment for preventing new onset postoperative atrial fibrillation in patients undergoing isolated coronary artery bypass grafting: a prospective randomized study" published in the June 2014 issue of Anatol J Cardiol (1). Our prospective randomized study with statin therapy regimen in the early postoperative period showed a statistically significant decrease in postoperative new-onset AF and a significant decrease in CRP levels in patients undergoing isolated CABG (1).

Preoperative statin therapy is also shown to reduce the incidence of postoperative AF (2, 3). Recently, CABG is frequently performed on the day after coronary angiography; therefore, preoperative statin therapy cannot be administered in most of the patients. Sakamoto et al. (2) detected a delay of approximately 2 days in the occurrence of AF in patients with preoperative statin therapy versus without statin therapy. The patients did not undergo preoperative statin therapy in our study, and we did not detect any difference in the occurrence day of the first postoperative AF. Therefore, we suggest that statin therapy should be started preoperatively, if possible (1). ARMYDA-3 was the first randomized controlled trial to evaluate the impact of preoperative statin therapy on postoperative AF. This was the largest randomized study. Atorvastatin was administered 7 days before heart surgery. As a result, preoperative atorvastatin reduced the risk of postoperative AF (3).

Recent studies have shown that statins reduce the CRP level in 2 weeks (4-6). Sakamoto et al. (2) started the statin therapy in the preoperative period and have shown that statins reduce the CRP level on the seventh postoperative day. Moreover, other mechanisms may contribute to the clinical benefit of statins, antioxidant effects, direct antiarrhythmic effects by cell membrane ion channel stabilization, improvement of coronary flow velocity reserve by vasodilation of coronary micro vessels, rapid (<12 h after a single dose of atorvastatin) improve-

ment of endothelial function, or direct protection of the myocardium also plays a role in extracellular matrix modulation (3, 6). These effects may contribute to the prevention of AF of statins. Therefore, we suggest that routine administration of statins is useful in patients undergoing elective CABG for prevention of postoperative AF. In our study, CRP levels were significantly lower in patients without AF versus those with AF. CRP levels on the 14th postoperative day were significantly lower in the statin group compared with those in the non-statin group.

Atorvastatin undergoes rapid absorption when taken orally, with an approximate time to reach maximum plasma concentration (Tmax) of 1-2 h. The absolute bioavailability of the drug is approximately 14%; however, the systemic availability for HMG-CoA reductase activity is approximately 30% (7). Thus, based on pharmacokinetics, the drug should be active and effective during the first postoperative day. Each extubated patient was given 40 mg of atorvastatin per day, which was started on an average of 6 h after the operation. All patients are able to take oral statin. Therefore, we suggest that if preoperative statin therapy is not administered to patients, statin therapy should be started in a short time postoperatively to obtain the beneficial effects of statins.

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Frequently occurring Torsades de pointes attacks in an old patient on solifenacin therapy and management strategy

To the Editor,

The most frequent reason for the acquired long QT syndrome and associated Torsades de pointes (TdP) is drugs. Solifenacin, an antimuscarinic drug, causes QT prolongation by decreasing the activity of potassium channels in phase 3 of the action potential (1). In these patients, temporary pacemaker (PM) implantation is a life-saving therapeutic approach (2).

An 84-year-old male patient was admitted to the emergency department with complaints of short-term episodes of loss of consciousness and cyanosis in the hands. The patient has been on treatment with 10 mg/day solifenacin for 15 days because of the urinary incontinence. In addition, he has been taking metformin (2000 mg/day) and atorvastatin (10 mg/day) for type 2 diabetes mellitus and hyperlipidemia. The patient's consciousness was clear in the first examination in the emergency department. Moreover, it was determined that the patient had a blood pressure of 120/80 mm Hg, heart rate of 72 bpm, and blood glucose of 140 mg/dL. During evaluations, he developed a sudden loss of consciousness. A sustained ventricular tacycardia (VT) attack was observed in the electrocardiogram (ECG) monitor, and synchronized cardioversion was applied with 50 J. After cardioversion, a normal sinusal rhythm was established, and the patient's consciousness normalized again. A 12-lead ECG was obtained just after the VT episode. There were no ischemia-related alterations in 12-lead ECG; however, QT prolongation was determined. The corrected QT (QTc) interval was calculated as 548 ms. Cardiac enzymes and electrolytes were found to be in normal ranges. Despite the fact that the level of K+ was 4 mE/L, parenteral K^+ and peroral magnesium treatment were provided to the patient because of the existence of VT resulting from QT prolongation. Echocardiographic examination of the patient demonstrated normal echocardiographic findings with an ejection fraction of 63%.

Frequent VT attacks reappeared after approximately 4h. Short-term episodes of a loss of consciousness accompanied those attacks. Parenteral magnesium therapy was initiated. Because of the unresponsiveness of VT attacks to the parenteral magnesium treatment, synchronised cardioversion was applied 8 times. Sustained VT episodes were reappearing in almost 5-10 min after cardioversion. A temporary VVI-PM was implanted in the patient. The heart rate was set as 110 bpm in PM. The VT attacks did not recur after PM implantation. In addition, coronary angiography was performed to rule out coronary artery disease. The angiography demonstrated no significant obstructive lesion in epicardial coronary arteries.

When PM was stopped after 8 h, QTc was determined to be 450 ms. Serum electrolytes were also in normal ranges at that moment. On the next day, solifenacin therapy was discontinued. TdP attacks did not recur. Temporary PM was removed after 24 h of observation. The patient was discharged after 3 days of hospitalization. He had no complaints in the outpatient controls, and the QT interval was measured as 420 ms.

In conclusion, patients taking QT prolonging drugs should be monitored in the hospitals for few days in case of TdP development. After documenting the first TdP attack, temporary PM should be immediately inserted with a ventricular rate of 110-120 bpm to shorten the QT interval.