Editorial

The statin therapy to prevent atrial fibrillation after cardiac surgery: Shakespearean dilemma

Simone Calcagno, Rocco E. Stio, Massimo Mancone, Annalisa Pasquini, Erika Cavallo, Gennaro Sardella

Department of Cardiovascular, Respiratory, Geriatric, Anesthesiologic and Nephrologic Sciences, Umberto I Hospital, Sapienza University, Rome, Italy

Correspondence to: Gennaro Sardella. Department of Cardiovascular, Respiratory, Nephrologic, Anesthesiologic and Geriatric Sciences, Policlinico Umberto I, Sapienza University of Rome, Viale del Policlinico 155, 00186 Rome, Italy. Email: rino.sardella@uniroma1.it.

Submitted Oct 03, 2016. Accepted for publication Oct 12, 2016.
doi: 10.21037/jtd.2016.11.69
View this article at: http://dx.doi.org/10.21037/jtd.2016.11.69

Surgical and perioperative care are much improved in the last years but postoperative complications after cardiac surgery remain frequent, which are directly involved to increase the mortality, morbidity, and costs (1). Atrial arrhythmias and atrial fibrillation (AF) in particular are well-known complications after cardiac surgery with a reported incidence between 10% and 60% (2). Postoperative atrial arrhythmias extend the hospitalization, decreasing the hemodynamic condition and increasing the risk of stroke and mortality (3). The incidence is higher in patients undergoing valve surgery than in patients undergoing coronary artery bypass surgery (CABG) (4). Despite lower, post-operative atrial arrhythmias also occur after non-cardiac surgery (from 0.3% to 29%) (5,6), especially after oesophagectomy (7), lung surgery (6), and large abdominal surgery (8).

The exact pathophysiological mechanisms responsible for the onset and the perpetuation of post-operative atrial arrhythmias are incompletely understood and multiple theories have been advanced. The two principal factors facilitating post-operative AF (POAF) are differentiated in surgery related factors and pre-existing ones due to chronic and progressive process of heart remodeling (e.g., the increasing of left atrial volume) (9). These predisposing causes, together or alone, are the principal triggers to rationalize the development of atrial arrhythmia and the persistence of AF.

The association of POAF with specific types of surgery and the time course of the arrhythmia can be explained by two mechanisms. Firstly, the entity of cardiac surgical trauma and the degree of pre-existing cardiac pathology seems to be directly involved in the association of POAF and cardiac surgery. Secondly, the arrhythmia follows a specific time course with a major incidence in the second day after surgery with a rapidly decline to around 2% at discharge (9). This suggests that some of the pro-arrhythmic mechanisms need specific time to go in action but the transient nature of the arrhythmia suggests a reversible mechanism, caused by factors, which come into play shortly after surgery.

Actually inflammation and oxidative stress have been recognized to be on the basis of the pathogenesis of AF and other post-operative complications of cardiac surgery (10). Indeed, the incidence of POAF coincides with the peak of the systemic inflammatory response after cardiac surgery (10) and has been reported to be partially prevented by anti-inflammatory drugs (11,12).

Many data support the pleiotropic effect of statins showing a rapid anti-inflammatory and antioxidant effects with consequently a myocardial protection by reperfusion damage (13,14). The concentration of C-reactive protein after statin therapy, decrease in some studies (15-17). Perioperative statin therapy has been associated with a lower incidence of AF after cardiac surgery, as well as less severe myocardial injury preserved left ventricular and renal function, and shorter stays in the intensive care unit (ICU) and hospital (18).

On the basis of this evidence, practice guidelines currently recommend perioperative statin therapy for the prevention of AF and other in-hospital complications after cardiac surgery (19).

We read with big interest the recently published trial designed by Zheng *et al*. (Perioperative Rosuvastatin in

Cardiac Surgery trial) (20). This is a large randomized, placebo-controlled trial that aimed to provide more definitive evidence regarding the effects of perioperative statin therapy on postoperative complications.

The patients included (1,922 patients) were predominantly men (female sex was 20.2% in patient treated with Rosuvastin and 21.3% with placebo) who were mean 59 years of age. All patient were scheduled to undergo elective coronary-artery bypass grafting (CABG), surgical aortic-valve replacement, or both were eligible if they were in sinus rhythm and were not taking antiarrhythmic medication (other than beta blockers). Patients were excluded if they had moderate or severe mitral-valve disease or known renal dysfunction [creatinine level, >2.3 mg per deciliter (200 µmol per liter)] or had contraindications to statin therapy.

Any prescribed statin therapy was stopped, and patients were then randomly assigned to receive rosuvastatin at a dose of 20 mg once daily or matching placebo tablets for up to 8 days before surgery and for 5 days thereafter. The two pre-specified co-primary outcomes were postoperative AF and perioperative myocardial injury. Secondary outcomes were postoperative AF diagnosed clinically, alternative measures of myocardial injury, major in-hospital cardiovascular events and death, duration of ICU and hospital stay, the low cardiac output syndrome, pleural effusion, infection, left ventricular ejection fraction at discharge, acute kidney injury, and blood biomarkers.

A total of 87% of the patients underwent CABG surgery (including 3% who, in addition, had aortic-valve replacement), 10% underwent aortic-valve replacement alone, and 1% underwent some other type of surgery; 55% of the operations were on-pump.

The concentrations of both LDL cholesterol and high-sensitivity C-reactive protein were significantly lower in patients assigned to rosuvastatin than in those assigned to placebo.

Primary outcomes

Confirming the high rate of POAF, the treatment with rosuvastatin was not associated with a lower incidence of arrhythmia as compared with placebo (21% in the rosuvastatin group and 20% in the placebo group).

Rosuvastatin failed to show a significant effect on the incidence of POAF in any of the prespecified subgroups as in who started the trial regimen more than 2 days preoperatively, in who started the regimen 4 to 8 days preoperatively and in patients with a body-mass index of more than 25, those with a history of myocardial infarction, or those with a left ventricular ejection fraction of 55% or less. For the coprimary outcome of perioperative myocardial injury, rosuvastatin had no significant effect on troponin I release after surgery as on secondary outcomes related to myocardial injury. In-hospital adverse outcomes were monitored until discharge. AF was identified clinically by means of routine electrocardiography or assessment of symptoms in 16% of the patients in the rosuvastatin group, as compared with 12% of those in the placebo group (P=0.03). The mean creatinine plasma level was significantly higher in the rosuvastatin group than in the placebo group with excess at stage 1, 2 or 3 acute kidney injury. Otherwise, there were no significant differences between groups in the rates of recorded post-operative serious adverse events, in the duration of ICU stay or hospital stay, or in echocardiographic variables.

Discussion

In previous smaller clinical trials were found large differences in outcomes in terms of the occurrence of AF after cardiac surgery. Zheng with this large trial, weakens the current recommendation of perioperative statin therapy before surgery and its beneficial effect to decrease the incidence of POAF. Nevertheless, from the numerous experimental and epidemiological studies addressing the mechanisms of POAF, several conclusions can be drawn. Indeed, transient factors related to surgery as well as factors developing slowly and progressively contribute to the occurrence of POAF.

The time course of POAF underlines the importance of temporary surgery-induced factors as inflammation, sympathetic stimulation, and oxidative stress. Nevertheless, many surgical patients do not develop POAF, emphasizing that transient factors cannot be the only responsible mechanism for the occurrence of the arrhythmia.

The likeness between the time course of AF occurrence after cardiac surgery and the activation of the complement system with the release of pro-inflammatory cytokines suggests an inflammatory component in the mechanism triggering POAF (21). Complement activation during cardiac surgery with cardiopulmonary bypass (CPB) occurs in two steps. The first phase is mediated via the 'alternative pathway' and occurs during CPB by the interaction of blood with the surface of the extracorporeal circuit. The second phase acts via the 'classical pathway', starting with

protamine administration after CPB.

Comparison of AF incidence after off-pump and on-pump surgery facilitates to distinguish the importance of systemic inflammation from that of surgical incision and manipulation. As such, off-pump CABG (OPCAB) is believed to elicit less systemic inflammation than on-pump surgery because of reduced cytokine responses and less myocardial injury (22). However, the association between OPCAB and a lower incidence of atrial arrhythmias were not confirmed by several studies suggesting that surgical stress is more important triggering of POAF than systemic inflammation (22). These results need to interpretation because some of these have a retrospective design with small sample size, and that they all showed at least a non-significant trend towards lower AF incidence in off-pump surgery. Moreover, it is known that chronic inflammation in patients can cause atrial structural remodelling predisposing to the occurrence of POAF. Finally pre-operative CRP level was associated with an increased risk of the arrhythmia after CABG (10); on the contrary, others studies did not confirmed this association (23).

The second theory regarding the development of atrial arrhythmia is based on sympathetic activation. Indeed, it seems that sympathetic activation, by altering atrial refractoriness and promoting ectopic activity, contributes to the onset of POAF. The fact that b-blockade does not abolish all episodes of POAF once more stresses the multifactorial aetiology of POAF (9). However, oral b-blocker therapy started at least 1 week before surgery remains the first choice in preventing POAF after cardiac surgery.

The third theory is based on the oxidative stress occurs from an imbalance between pro-oxidants and antioxidants in favour of the first ones. During reperfusion, increased production of reactive oxygen species takes place, leading to myocardial stunning, tissue damage, and cell death (9). The involvement of oxidative stress in the multifactorial mechanism of POAF has been further studied by administrating antioxidant drugs to patients undergoing heart surgery. Indeed, antioxidant drugs like ascorbic acid (24), N-acetylcysteine (25), nitric oxide (26), sodium nitroprusside (27), are reported to lower the incidence of POAF after cardiac surgery involving CPB use. Another argument supporting a causative relation between oxidative stress and POAF is the higher occurrence of the arrhythmia in the elderly because they are more susceptible for ischaemia/reperfusion injury with a more important damage than in young patients and this, in part, explains the higher incidence of POAF in this population (28).

Finally, it is not enough because the occurrence of POAF is also strongly determined by the pre-existence of an AF substrate. Despite the importance of transient surgery-induced factors, the majority of POAF cases occur in atria with a pre-existing AF substrate due to a long-lasting structural remodeling process. AF substrate can involve the ion channel alterations resulting in shortening and enhanced dispersion of atrial refractoriness; and heterogeneities in conduction due to interstitial alterations like, for example, accumulation of collagen fibres, inflammatory infiltration or amyloidosis (9). The relationship of both factors with the onset of POAF is major supported by the later occurrence of AF. This emphasizes the important role for more chronic factors, not directly linked to surgery but with the structural alteration of the heart.

On the basis of clinical evidence, practice guidelines currently recommend perioperative statin therapy for the prevention of AF and other in-hospital complications after cardiac surgery (19). However, these recommendations are based on randomized trials that were small and had other important limitations. An updated meta-analysis of the results from previously published randomized trials of perioperative statin therapy (15-18) showed an approximate halving of the incidence of postoperative AF with statins as compared with placebo. However, those trials involved small numbers of patients and had other important limitations. For example, only same of the trials were designed with a prespecified postoperative AF as an outcome (16,29,30), and only one trial (29) included an intention-to-treat analysis of the effect on AF as detected in a systematic and blinded manner. Furthermore, a recent systematic Cochrane review of those trials showed evidence of selective reporting and publication bias (31). The suggestion that perioperative statin therapy might be associated with less severe myocardial damage derives from one randomized, placebo-controlled trial involving 200 patients undergoing CABG surgery (32) and from a non-blinded randomized trial involving 151 patients undergoing non-coronary cardiac surgery, which also reported improved left ventricular function (17).

Conclusions

The beneficial effect of statin therapy to reduce the inflammation, sympathetic stimulation and oxidative stress has been demonstrated by *in vitro* studies. In clinical trials were found large differences in outcomes as showed above.

These differences do not provide a consistent indication of the efficacy of perioperative statin therapy to reduce the incidence of AF and other arrhythmias after cardiac surgery.

Acknowledgements

None.

Footnote

Provenance: This is an invited Editorial commissioned by the Section Editor Kefang Guo (Fudan University Zhongshan Hospital, Shanghai, China).
Conflicts of Interest: The authors have no conflicts of interest to declare.

Comment on: Zheng Z, Jayaram R, Jiang L, *et al*. Perioperative rosuvastatin in cardiac surgery. N Engl J Med 2016;374:1744-53.

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Cite this article as: Calcagno S, Stio RE, Mancone M, Pasquini A, Cavallo E, Sardella G. The statin therapy to prevent atrial fibrillation after cardiac surgery: Shakespearean dilemma. J Thorac Dis 2016;8(11):2986-2990. doi: 10.21037/jtd.2016.11.69

