



Prophylaxis with amiodarone for postoperative atrial fibrillation: when and who?

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Post-operative atrial fibrillation (PoAF) is generally considered as a benign, self-limiting complication of cardiac surgery. However, it is associated with complications such as stroke, prolonged intensive care unit (ICU) stay and need for dialysis, leading to longer hospitalization and higher costs (1,2). Even in-hospital and long-term mortality are higher in patients who develop PoAF (2,3), making it clear that PoAF is less innocent than assumed.

Therefore, pathophysiology and prevention of PoAF have been topics of extensive research. In this issue of *Journal of thoracic disease (JTD)*, Mehaffey *et al.* (4) give a detailed report of their retrospective evaluation of cost-effectiveness of a prophylactic amiodarone protocol implemented to reduce the incidence of PoAF. They found a significantly reduced rate of PoAF and \$458 cost saving per patient with the implemented protocol. They did not observe a significant increase in risk-adjusted adverse events related to amiodarone.

The findings of cost saving by prevention of PoAF with amiodarone are in accordance with prior studies (5-7), although this is the first cost-effectiveness analysis of a protocol-driven approach. The authors are to be complemented for their clear example of assessing cost-effectiveness of an implemented quality improvement protocol. Important to mention is the high percentage of patients who were treated according to the protocol. As also remarked by the authors, this can be attributed to the protocol starting immediately postoperatively. But correct timing of amiodarone prophylaxis is a matter to consider.

Timing and dosage of amiodarone

Research into the pathophysiology of PoAF has identified chronic and acute factors at play (8). As soon as the surgeon cuts in the patient's tissue the acute factors, related to the surgical intervention, become relevant. Therefore, it would be rational to presume that appropriate tissue levels of amiodarone at this moment in time are a prerequisite for maximal prevention of PoAF. However, two meta-analyses focusing on the timing of amiodarone administration did not find a difference between a post-operative or pre-operative start of amiodarone in coronary artery bypass graft (CABG) patients (9,10). A possible explanation for this is that onset of PoAF is typically 2-3 days after cardiac surgery (2). This suggests that pro-arrhythmic mechanisms related to the surgery, such as inflammation, oxidative stress and sympathetic activation, reach their maximum impact at this time. Therefore, starting amiodarone immediately post-operatively, allows enough time to reach the adequate tissue levels.

Dosage and route of administration of amiodarone were discussed in meta-analyses by Buckley *et al.* and Chatterjee *et al.* respectively. Total prophylactic amiodarone dosage above 3,000 mg was found to be effective by Buckley *et al.* (9). Chatterjee *et al.* did not find a difference between regimens with only oral amiodarone or a combination of oral and intravenous amiodarone (10). By these standards, the regimen used by Mehaffey *et al.* is appropriate.

When addressing the timing of initiation of the protocol,

differences in clinical endpoints are of importance. In the current study, it was reported that length of hospital stay and major morbidity in the two groups were not significantly different. Yet, clinical endpoints for interventions reducing PoAF incidence were analyzed in various meta-analyses showing positive effects for amiodarone prophylaxis on incidence of stroke, occurrence of ventricular tachycardia and length of hospital stay (7,11,12). However, these meta-analyses did not divide the studies in pre or post-operative start of amiodarone prophylaxis. Prior studies with a pre-operative as well as a post-operative start of amiodarone protocol showed a significant reduction in length of stay (13-15). Yet, a lower incidence of post-operative stroke was only found in regimens starting pre-operatively (16). So far, there are no reports on the different timing of the prophylaxis in relation to these hard-clinical endpoints, though they are needed to further validate the use of the various protocols.

Substrate of PoAF

Some patients have a higher risk of developing PoAF than others and various risk factors have been determined (2). Distinguishing patients at risk could improve the benefit of implemented protocols. One retrospective observational analysis by Barnes *et al.* used a previously validated risk score for PoAF to investigate cost-effectiveness of amiodarone prophylaxis. Patients were stratified into 3 risk groups according to risk-increasing variables such as advancing age, a history of COPD or undergoing heart valve surgery. Also, risk-decreasing variables such as postoperative beta-blocker use were taken into account. They found that the greatest benefits were seen in patients at high risk for developing PoAF, and in that group prophylaxis was most cost-effective (17).

As mentioned above, acute as well as chronic factors contribute to development of PoAF. Determining the presence of these chronic factors or, as you could say, determining the presence of an arrhythmogenic substrate for PoAF in the atria could more accurately pinpoint patients at risk. A considerable amount of electrophysiological mapping studies is aimed at identifying the electrophysiological substrate of atrial fibrillation, although studies focusing on the substrate of specifically PoAF are rare. Sakamoto *et al.* obtained epicardial recordings of the right atrium in sinus rhythm from 52 patients. These patients underwent cardiac surgery for valvular disease, ischemic heart disease or a congenital heart disease. They found that a non-uniform activation pattern was a significant independent predictor

for PoAF (18). Teuwen *et al.* performed high-resolution epicardial mapping of Bachmann's bundle (BB) during sinus rhythm in 185 patients during coronary artery bypass surgery and found that a high amount of conduction block was associated with PoAF (19).

In discovering what (electrophysiological) features of the atria define the substrate for PoAF, our understanding of the pathophysiology will grow and we can more accurately predict which patient will develop PoAF and which patient will not.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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