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## Editorial comment

Keywords: Aprotinin; Cardiac surgery; Mortality; Late survival

Stamou and colleagues present another critical article about adverse outcome following administration of aprotinin in adult cardiac surgery [1]. In this retrospective study, haemostatic effects of aprotinin were confirmed but the authors found an increased risk for in-hospital cardiac arrest. Another intriguing finding was found, namely that the risk of late cardiac death was higher in patients who received aprotinin than after aminocaproic acid (EACA). Unfortunately, neither the cause of early mortality nor the problem of cardiac-related attrition (graft occlusion, perioperative myocardial infarction, malignant arrhythmias or others) were analysed or specified.

Because of the retrospective character of the study, several limitations and bias have to be considered: the use of aprotinin or EACA was left at the discretion of the surgeons. The patients who received aprotinin were older, had more prior surgery, suffered more frequently from congestive heart failure (NYHA class IV) and underwent more often complex and emergency surgery than those who received EACA. It is questionable if propensity score matching may be sufficient to eliminate 'confounding by treatment' differences of the two study groups. The authors conclude that the risk of aprotinin may not be worth the benefit of reduced transfusion requirements.

There are a tremendous number of publications dealing with aprotinin, but a single finding seems to be consistent: aprotinin is associated with decreased transfusion requirement and re-exploration rate because of bleeding. This was already the main finding of the initial report of Royston and colleagues [2]. In more recent years, the question appeared if aprotinin increases the risk of renal dysfunction and is an independent predictor of increased mortality. Concerning the last two end-points, conflicting results are present in literature.

The two most important 'negative' trials for aprotinin (Mangano et al. [3] as well as the Bart trial [4]) have been

largely discussed in literature. Not only the power but also the limitations of these trials are very well pointed out. Some authors believe that the recent 'attacks' against aprotinin may have been statistically unsound [5]. Even extensive meta-analysis of the Cochrane collaboration in 2007 have not found an increased risk of death caused by the use of aprotinin compared to lysine analogues. The use of aprotinin was recommended especially in high-risk patients in whom a substantial blood loss has to be expected [6]. In a more recent update, this option has been contradicted by the same authors [7].

What are the remaining questions? There has been an increasing concern that questions the safety of aprotinin. If we accept this, we are forced to ask why this was not detected during the two decades of extensive use of the drug with published good results. As a result of the aprotinin story [8], studies should – if ever possible – focus on clinical end-points that are not confounded with surrogate markers. Independent clinical safety studies are mandatory even after regulatory approval.

Unfortunately, the large majority of studies that demonstrated adverse outcome following aprotinin were performed using the original Hammersmith protocol, which means a high dosage. More than 15 years ago, we published similar beneficial haemostatic results with low-dose aprotinin and no adverse cardiac outcome was observed, neither early nor late [9]. We do not understand why the low-dose regime was not adopted by more institutions.

Finally, it is today still not clear which patient subgroups may benefit from aprotinin. However, this is more of theoretical interest since the drug is no longer available on a regular basis. Considering that low-risk cardiac surgical patients are at increased risk for bleeding events (e.g., having operation under ongoing combined anti-platelet therapy), other potent measures in addition to the available lysine analogues in order to reduce postoperative bleeding,

the need for transfusion and the incidence of haemorrhagic re-exploration are welcome.

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