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PRO: Should aspirin be continued post-cardiac surgery in the setting of thrombocytopenia?

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Aspirin is one of the most cost-effective therapies available for the prevention and treatment of platelet-mediated vascular occlusive disorders, which consist of a heterogeneous group of diseases including myocardial infarction (MI), stroke, and vascular graft thrombosis. In a meta-analysis of 195 randomized clinical trials that included over 140,000 high risk patients, aspirin-treated patients had a 22% reduction (10.7% vs. 13.2%, $P < 0.0001$) in the risk of MI, stroke, or death[1]. The absolute benefit of anti-platelet therapy far exceeded the excess bleeding risk, which was 1.13% vs. 0.71% ($P < 0.0001$), and the vast majority of aspirin-related bleeding events were nonfatal[1].

The therapeutic benefit of aspirin is thought to be related to its anti-platelet action. Aspirin causes irreversible acetylation of platelet cyclooxygenase-1 (COX-1), impairs platelet generation of thromboxane, and thereby inhibits thromboxane-dependent platelet activation and vascular occlusion. Because acetylation is irreversible, and because platelets have limited capacity for translation of new protein, inhibition of COX-1 activity lasts for the life-span of the platelet – approximately 7–10 days. However, the anti-platelet action of aspirin is only partial. Platelet activation may occur along numerous COX-1-independent pathways, and aspirin has limited or no impact on these events. Aspirin's incomplete anti-platelet action limits its therapeutic efficacy when more intense anti-platelet activity is desirable (e.g., in acute coronary syndromes and after percutaneous coronary intervention)[2,3], and also limits its capacity to cause bleeding complications. The failure of aspirin to prevent vascular occlusive events has recently generated intense interest. Aspirin's clinical failure and its inability to inhibit platelet function in vitro have both been termed "aspirin resistance". Zimmerman et al[4] reported that a high proportion of coronary artery bypass graft (CABG) patients develop aspirin resistance by postoperative day 5, and suggest that this effect may be overcome by more intense anti-platelet therapy.

The major indication for aspirin after cardiac surgery is to reduce the incidence of vein graft occlusion after CABG. In a meta-analysis of 20 randomized clinical trials that included more than 5000 patients who underwent CABG, anti-platelet therapy reduced the proportion of patients who suffered graft occlusion by 41% (21.1% vs. 30.3%, $P < 0.00001$)[5]. Improved graft patency occurred whether aspirin was started preoperatively or immediately postoperatively[5], and persisted at one year when aspirin treatment was continued[6,7]. However, aspirin does not appear to improve graft patency if started more than 72 hours after surgery[8,9]. The ability of aspirin to prevent MI, stroke, and death in CABG patients is less certain based on data from meta-analyses[1]. However, in a recent retrospective analysis, CABG patients treated with aspirin within the first 48 postoperative hours had a lower incidence of postoperative MI (2.8% vs. 5.4%, $P < 0.001$), congestive heart failure (5.8% vs. 11.0%, $P <$

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0.001), and death (1.3% vs. 4.0%, P < 0.001) compared to patients who did not receive aspirin[10]. Complications of aspirin after CABG appear to be insignificant. In trials in which aspirin was started postoperatively, the observed incidences of fatal bleeding, nonfatal bleeding, reoperation, and hematoma-related complications were no different from placebo[5].

How then should aspirin therapy be managed in CABG patients who develop postoperative thrombocytopenia? After defining "thrombocytopenia" and assessing the frequency with which it occurs after cardiac surgery, one can extrapolate from the available data to craft a management strategy. A normal platelet count is 150,000 – 400,000 per microliter, which far exceeds the number of platelets required to achieve hemostasis. Spontaneous bleeding does not occur until severe thrombocytopenia develops – somewhere around 10,000 platelets per microliter. By American Society of Anesthesiology consensus guidelines, a platelet count between 50,000 and 100,000 per microliter is considered adequate for hemostasis when invasive procedures are planned. Higher platelet counts may be needed if concurrent thrombocytopenia and platelet dysfunction are present in the setting of active bleeding.

Using normal standards, thrombocytopenia after cardiac surgery is virtually ubiquitous. Platelet counts fall from the normal range to a mean of approximately 100,000 per microliter (1 SD ~ 20,000/microliter) immediately after cardiopulmonary bypass, and remain <150,000 for 4–5 days[11]. Despite the concurrent presence of thrombocytopenia and platelet dysfunction, adequate hemostasis is achieved in the vast majority of CABG patients intraoperatively or within the first several postoperative hours, albeit after transfusion of platelets and/or FFP in a substantial proportion of patients. It is precisely in this setting of near universal thrombocytopenia that randomized clinical trials of early postoperative aspirin therapy showed improved graft patency without increased risk of bleeding. Thus, based on available evidence, the routine use of aspirin after CABG seems warranted.

It is important to note that moderate to severe thrombocytopenia (platelet count < 50,000 per microliter) is relatively uncommon after cardiac surgery. It is difficult to extrapolate from published studies to management of such patients. In most cases, the development of this degree of thrombocytopenia is a sign of another underlying problem – e.g., sepsis, heparin-induced thrombocytopenia, presence of mechanical circulatory support, drug reaction, etc. – and many of these conditions are also associated with a propensity for platelet-mediated thrombosis. In such patients, diagnosing the cause of thrombocytopenia and institution of definitive treatment are the priority. Aspirin can probably be safely continued in such patients unless clinical bleeding occurs, or until the platelet count falls to 10,000 – 20,000 per microliter.

In summary, randomized clinical trials and meta-analyses strongly support the routine use of early postoperative (< 72 hours) aspirin therapy in CABG patients to improve coronary vein graft patency, despite the near universal presence of mild to moderate thrombocytopenia. Retrospective studies indicate that early postoperative aspirin therapy is associated with decreased morbidity and mortality. The development of more severe thrombocytopenia after cardiac surgery should prompt a search for the underlying cause and institution of appropriate therapy. Aspirin should be stopped if clinical bleeding occurs or when the risk of spontaneous bleeding becomes unacceptably high.

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