Editorial

Venous thromboembolism prophylaxis after minimally-invasive cardiac surgery: harm or benefit?

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The term venous thromboembolism (VTE) encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE), which may have a major impact on the postoperative outcome after surgery. These severe complications are associated with high morbidity and mortality, to an increase in hospital length of stay and costs, and are a major cause of hospital readmission (1). Strategies to prevent the onset of DVT and PE after surgery are therefore of utmost importance. Current international guidelines recommend DVT prophylaxis in the immediate postoperative period after general, orthopedic and thoracic surgery. In these settings, prophylaxis with heparin, low-molecular weight heparin (LMWH), fondaparinux or with compression stockings is associated with a significant reduction of the incidence of postoperative DVT and PE and to an improvement of postoperative morbidity and mortality (2). Conversely, the cost-effectiveness of VTE prophylaxis after cardiac surgery is still a matter of debate, since these patients are considered at medium risk for DVT and PE and at potentially high risk of hemorrhagic complications (3).

In the study by Li *et al.*, the pros and cons of DVT prophylaxis with LMWH after minimally-invasive valve repair by partial sternotomy or mini-thoracotomy were evaluated in a propensity score-matched analysis. Data of a group of 257 patients receiving prophylaxis with LMWH in the early postoperative period were compared with those of a group of 216 patients who were not treated with LMWH. The main outcome measures included the incidence of embolic and major bleeding events. Length of stay, time to chest drain removal and poor wound healing were also analyzed. Before propensity score matching, fewer embolic events were observed in patients undergoing DVT prophylaxis, although these data did not reach statistical significance. However, after propensity score matching no significant advantages concerning the incidence of VTE were found in the LMWH group. Conversely, the Authors observed a significantly higher incidence of major bleeding events, volume of drained fluid, duration of chest tube placement, impaired wound healing and postoperative hospital length of stay in the group submitted to prophylaxis. The conclusions of this study are therefore that, although with some limitations as the relatively limited size of the trial and the fact that only patients with valvular disease were included in the study, VTE prophylaxis after minimally-invasive cardiac surgery may not be beneficial (4).

The data of this study certainly are to be confirmed in larger trials, but nevertheless raise an important point, as the need to analyze the cost-effectiveness of VTE prophylaxis in specific subgroups of patients undergoing cardiac surgery. In a recent study, Khoury *et al.* analyzed the data of more than three million patients submitted to cardiac surgery recruited from the National Inpatient Sample (NIS) database, and observed that DVT and PE had an incidence of 1.62% and 0.38%, respectively. Noteworthy, PE was associated at multivariate analysis with an increase of postoperative mortality, hospital length of stay and hospitalization costs.

A higher incidence of renal, respiratory and cardiovascular complications was also observed in patients with DVT and PE (5). In another study, Du *et al*. analyzed a series of 8,956 patients from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) submitted to coronary artery bypass grafting (CABG). In this study, postoperative VTE was observed in 1.75% of the patients, with an incidence of PE and deep vein thrombosis of 0.61% and 1.28%, respectively. The results of this study confirmed that patients who developed DVT and PE had worse postoperative outcomes and a higher risk of re-operation, length of stay and hospital readmission. The occurrence of VTE was also associated with a higher incidence of postoperative complications as the need of emergency intubation, an increased time of mechanical ventilation, pulmonary and urinary tract infections, transfusion requirement and renal failure (6). Although these data clearly demonstrate the clinical relevance of VTE after cardiac surgery and therefore the need of strategies to prevent this complication, other studies have failed to demonstrate the cost-effectiveness of VTE prophylaxis. Accordingly, a definite consensus on the indications for DVT prophylaxis after cardiac surgery has not yet been reached. In fact, in another study, Kulik *et al*. analyzed a cohort of over 90,000 patients submitted to on-pump and off-pump coronary artery bypass surgery, and observed that the use of heparin, LMWH or mechanical compression stockings did not significantly reduce the risk of VTE, although also not significantly increasing the incidence of hemorrhagic events (7).

Current international guidelines are also heterogeneous. The European Association for Cardiothoracic Surgery (EACTS) 2008 guidelines state that prophylaxis for VTE is to be commenced from the first postoperative day after cardiac surgery (8). On the other hand, the 2012 American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis consider that patients after cardiac surgery are at high risk of major bleeding complications, and are only at moderate risk for VTE. According to the ACCP guidelines pharmacological VTE prophylaxis is therefore indicated in case of a prolonged hospitalization after surgery. However, these Grade-2C recommendations are essentially based on consensus among experts, with a weak level of evidence (2). According to the National Institute for Health and Clinical Excellence (NICE) guidelines, prophylaxis after cardiac surgery should consist of mechanical compression in the absence of risk factors, and LMWH should be associated to mechanical prophylaxis if specific risk factors for DVT are present, provided that the patient is not treated with other anticoagulant drugs (9). The disparity of the results of previous studies and of current guidelines reveal that several issues concerning the role of VTE prophylaxis after cardiac surgery still have to be defined.

A first point concerns the actual incidence of DVT and PE, which may be significantly underestimated. This is mainly due to the fact that specific assessments to confirm the diagnosis of DVT or PE are usually carried out only when clinical signs or symptoms are observed. In a study performed by Viana *et al*. computed tomographic angiography and lower extremity venous ultrasound were systematically performed in a group of 100 patients submitted to on-pump and off-pump coronary artery by-pass surgery. The patients included in the study were not submitted to postoperative DVT prophylaxis, and those with a high risk for DVT were excluded from the analysis; antiplatelet therapy was maintained perioperatively and early ambulation was encouraged. PE was diagnosed in 13% of the patients, DVT in 4% and both PE and DVT in 8% of them, for a total VTE incidence of 25%. Notably, a significant number of patients was asymptomatic and would have been discharged from the hospital without further treatment (10). A point to be considered concerns the fact that DVT may not be clinically significant in all patients, considering that most of the patients submitted to cardiac surgery are postoperatively treated with antiplatelet or anticoagulant drugs, which may contribute to a reduction of the clinical impact of VTE.

Another main issue to be addressed concerns the fact that not all patients undergoing cardiac surgery have the same risk of developing DVT and PE, a point which may pose significant limitations in the comparison of the results between different studies analyzing the role of VTE prophylaxis. In fact, the incidence of risk factors for DVT and PE as advanced age, obesity and comorbidities may vary among different trials. Moreover, surgical techniques (open and mini-invasive, off-pump and on-pump), type of cardiac disease and postoperative anticoagulant or antiplatelet treatment schedules may also be diversified.

Other specific issues need to be considered, as the prothrombotic state that has been described after cardiac surgery due to factors as increased fibrinogen concentrations, thrombin generation, tissue factor activation and reduced fibrinolysis (11). The benefit of performing off-pump surgery seems to be limited, since

Parolari *et al*. observed that patients undergoing off-pump surgery had a reduced activation of coagulation and endothelial injury intraoperatively, but subsequently developed a prothrombotic pattern that was similar to that observed after surgery with extracorporeal circulation (12). The type of cardiovascular disease may also influence the risk of postoperative VTE. In the study by Khoury *et al*. the mortality in patients that developed DVT and PE was 4.95% and 14.8%, respectively. Higher mortality rates were observed after valve replacement surgery than after CABG. This finding may be justified by the higher incidence of comorbidities in patients with valve disease, that was directly correlated with the incidence of VTE (5). Other factors may increase the risk for VTE: Du *et al*. observed that patients undergoing CABG who developed DVT had an American Society of Anesthesiologists classification ≥3 or a body-mass index >35 kg/m^2. Longer operative times, bleeding disorders and congestive heart failure within 30 days before surgery were also risk factors for the development of postoperative VTE (6).

Seeking for an optimal and cost-effective approach for VTE prophylaxis after cardiac surgery, another important issue to be considered is the surgical approach. Minimally-invasive techniques have been increasingly introduced in clinical practice in the last decades (13). The main advantage of these approaches is related to a reduced surgical trauma, better pain control, earlier postoperative ambulation and a shorter length of stay. Enhanced recovery after surgery (ERAS) pathways including minimally-invasive cardiac surgery have reached favorable results in terms of hospital length of stay and cost reduction (14). However, the impact of minimally-invasive cardiac surgery on the incidence of postoperative DVT and PE and the definition of the risk-benefit ratio of VTE prophylaxis in this specific setting has yet to be defined. In fact, the potentially favorable impact of minimally-invasive procedures on the thrombotic risk has to be weighed against specific risks for DVT and PE. As a matter of fact, percutaneous cannulation of the femoral vessels, frequently used to perform cardiopulmonary bypass during minimally-invasive surgery, may be associated with endothelial lesions and impaired distal venous blood drainage, potentially increasing the risk of thrombosis.

Thus, a stratification of the patients according to the specific disease, surgical approach and risk factors for DVT and PE could potentially allow to identify the subgroups of patients in whom VTE prophylaxis could be cost-effective. In particular, since a higher use of percutaneous and minimally-invasive approaches is to be expected in the next years, this specific setting requires special attention.

In conclusion, due to the lack of a detailed risk stratification for VTE in patients undergoing cardiac surgery and to the influence that factors as the type of disease, surgical procedures (open and minimally-invasive, on-pump and off-pump surgery) may have on the incidence of DVT and PE, the cost-effectiveness of VTE prophylaxis after cardiac surgery needs to be further investigated. Present guidelines consider cardiac surgery patients at moderate risk of VTE, and are therefore cautious in recommending standard prophylaxis with LMWH after cardiac surgery due to an increased risk of hemorrhagic complications. Mechanical prophylaxis with intermittent pneumatic compression (IPC) stockings is therefore generally advised, especially in patients with a high hemorrhagic risk, adding pharmacological VTE prophylaxis with LMWH only in patients with specific risk factors as advanced age, transfusion requirement and postoperative neurological, renal and septic complications, unless contraindicated by insufficient hemostasis (15). Nevertheless, in the search of guidelines further studies are advisable, to address in particular the risk and benefits of thromboprophylaxis after minimally-invasive and endovascular procedures, considering that a higher number of these procedures is to be expected in the near future.

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Footnote

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