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REVIEW

Direct oral anticoagulant use and stent thrombosis following an acute coronary syndrome: A potential new pharmacological option?

Utilisation des anticoagulants oraux directs et thrombose de stent a décours d'un syndrome coronaire aigu : une nouvelle option pharmacologique potentielle ?

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Summary With the evolution of techniques and pharmacological strategies in percutaneous coronary intervention, significant advances have been made towards reducing the risk of in-stent restenosis and improving patient outcomes. However, in spite of these advances, stent thrombosis remains a deadly complication of stent implantation. The fundamental challenge in implementing a combined anticoagulant and antiplatelet strategy is balancing the risk of bleeding with the enhanced efficacy of therapy on both pathways. Results from the ATLAS ACS 2—TIMI 51 trial suggest that the addition of rivaroxaban 2.5 mg twice daily to standard antiplatelet therapy may achieve this desired balance alongside careful patient selection. This review considers the clinical burden and pathology of stent thrombosis, oral antithrombotic strategies to reduce stent thrombosis, and what findings from recent trials could mean for the long-term management of patients with an acute coronary syndrome.

Abbreviations: ACS, acute coronary syndromes; bid, twice daily; CABG, coronary artery bypass graft; CI, confidence interval; DAPT, dual antiplatelet therapy; HR, hazard ratio; od, once daily; PCI, percutaneous coronary intervention.

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MOTS CLÉS
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Résumé Avec l'évolution des techniques percutanées et des stratégies pharmacologiques chez les patients bénéficiant d'une intervention coronaire percutanée, des avancées significatives ont été mises en avant pour réduire le risque de sténose intra-stent et donc d'améliorer le pronostic de ces patients. Cependant, malgré ces avancées significatives, la thrombose de stent demeure une complication potentiellement létale au décours de l'implantation d'un stent. Le pari essentiel est, malgré le traitement antithrombotique double, anticoagulant et antiplaquettaire, d'obtenir une balance favorable dans la prévention du risque de thrombose de stent, sans augmenter le risque de saignement. Les résultats des études ATLAS et ACS 2-TIMI 51 ont suggéré que l'adjonction de rivaroxaban à faible dose, 2,5 mg deux fois par jour, en sus du traitement antiplaquettaire standard, pourrait contribuer à contrebalancer les effets délétères sur la perméabilité du stent coronaire. Cette revue générale prend en considération le risque clinique et les conséquences pathologiques de la thrombose de stent, ainsi que l'efficacité des stratégies antithrombotiques afin de réduire cette complication, ainsi que les avancées des essais cliniques récents pour définir les modalités de prise en charge des patients au décours d'un syndrome coronaire aigu.

Introduction

Percutaneous revascularization has revolutionized the management of patients across the spectrum of coronary artery disease, from chronic stable angina through to acute coronary syndromes (ACS). Drug-eluting stents greatly reduced the risk of in-stent restenosis compared with bare-metal stents (or balloon angioplasty) [1—4]; however, stent thrombosis that occurred with these stents was often related to delayed endothelialization [5]. This relatively rare but serious complication of stent implantation created near-paranoia in the media and in the cardiology community, with reported rates of mortality for patients with stent thrombosis of up to 45% [6,7].

This review will explore the clinical burden and pathology of stent thrombosis in relation to the timing of an event, with a focus on the underlying role of thrombin in the fundamental process, and will reassess recent developments in antithrombotic therapy to reduce the risk of stent thrombosis.

Clinical burden and pathology of stent thrombosis

According to a recent article by Claessen et al. [8], the incidence of stent thrombosis up to 1 year post-stenting appears to be similar for bare-metal and drug-eluting stents, quoted as ranging from approximately 0.6% to 3.3%. However, there is some suggestion of higher rates of very late stent thrombosis with drug-eluting stents compared with bare-metal stents. In a 5-year follow-up study from the Netherlands of patients enrolled in the Paclitaxel-Eluting Versus Conventional Stent in Myocardial Infarction with ST-segment Elevation (PASSION) trial, there was a trend towards a higher incidence of definite or probable very late stent thrombosis (> 1 year) in patients receiving paclitaxel-eluting stents compared with bare-metal stents (3.5% vs 1.1%, respectively; $P = 0.06$), reaching statistical significance for definite very late stent thrombosis (3.3% vs 0.7%; $P = 0.04$) [9]. Another long-term US study in patients with ST-elevation myocardial infarction ($n = 1640$) reported incidence rates of stent thrombosis (definite, probable or possible) of 2.7% (0—30 days), 5.2% (at 1 year) and 8.3% (at 5 years) during the drug-eluting stenting period (2003—2009) [10], although these high rates may reflect the high-risk population included in this analysis. Drug-eluting stenting was also the only significant independent predictor of very late stent thrombosis (hazard ratio [HR] 3.77, 95% confidence interval [CI] 1.81—7.88; $P < 0.001$). Interestingly, a recent meta-analysis by Palmerini et al. [11] suggested that the incidence of the Academic Research Consortium defined definite stent thrombosis with a second-generation everolimus-eluting stent was significantly lower than with first-generation stents (paclitaxel, sirolimus and zotarolimus eluting, pooled data: 0.5% vs 1.3%, respectively; relative risk 0.38; 95% CI 0.24—0.59; $P < 0.0001$). Similar results were reported for Academic Research Consortium defined definite or probable stent thrombosis (relative risk 0.46, 95% CI 0.33—0.66; $P < 0.0001$).

The occurrence of stent thrombosis varies depending on a host of clinical patient characteristics, the type of stent used, and the type of adjunctive pharmacotherapy used acutely and chronically to prevent these events (Fig. 1). The patients profiled as having an increased risk of stent thrombosis include those with common comorbidities such as diabetes [12], renal dysfunction [6] and previous myocardial infarction [10]; patients with multiple stents implanted, especially those of long length and narrow diameter [13]; and patients with poor compliance to medical therapy, including dual antiplatelet therapy (DAPT; aspirin plus a $P2Y_{12}$ inhibitor) [6,14]. Additionally, the specifications of various stents, including stent strut thickness, type and thickness of the polymer coating, and the antiproliferative therapy required, have also been linked to an increased risk of stent thrombosis [15].

Despite relatively low incidence rates of stent thrombosis, the case-fatality rate with stent thrombosis remains high. One-year mortality rates of approximately 10—25% in patients with stent thrombosis have been reported [16]. More recently, the findings from an analysis of data from