Intern Emerg Med (2013) 8:537–538
DOI 10.1007/s11739-013-0951-9

THE CUTTING EDGE: RESEARCH UPDATE

Anti-thrombotic treatment in patients with a long-term indication for anticoagulant therapy undergoing coronary stenting

Elisa Maria Fiorelli · Mattia Bonzi · Gruppo di Autoformazione Metodologica (GrAM)

Received: 30 March 2013 / Accepted: 20 April 2013 / Published online: 1 May 2013

Background

In patients undergoing percutaneous coronary intervention (PCI) with a stent implantation, double antiplatelet therapy for at least 1 month, according to stent type, is recommended to prevent stent thrombosis [1]. Nevertheless 5–10 % of these patients with ischaemic heart disease have a concomitant indication for oral anticoagulants (OAC) (i.e., mechanical heart valves, atrial fibrillation and venous thromboembolism) [2–4].The association of OAC and antiplatelet agents leads to an increased risk of fatal and non-fatal bleeding events [5]; in particular triple therapy (OAC + aspirin and clopidogrel) is associated with a prevalence of 12-months major bleeding of 7.4–10.3 % [3]. Nowadays the optimal anti-thrombotic therapy of patients already taking OAC and undergoing a coronary stent implantation is still not well defined when considering both the thrombotic and the bleeding risk. The results of a recent meta-analysis show that triple therapy is associated with a significant reduction in the incidence of thrombotic events even though there is a two-fold increase of bleeding episodes [6]. Despite little evidence being available, experts recommend the implantation of bare-metal stents and prescription of triple anti-thrombotic therapy for as short a period as possible in patients with chronic OAC undergoing coronary stenting.

E. M. Fiorelli (✉) · M. Bonzi
Ospedale Luigi Sacco, Università degli studi di Milano, Milan, Italy
e-mail: elisafiorelli@live.it

Summary

Dewilde et al. conducted an open-label, multicentre, randomized, controlled trial evaluating the bleeding risk in patients taking OAC and undergoing PCI with stent implantation. Patients were considered eligible if they had a long-term indication for oral anticoagulation treatment (until at least 1 year after the study), a severe coronary lesion with indication for PCI and age of 18–80 years. Exclusion criteria were history of intracranial bleeding; cardiogenic shock; contraindication to use of aspirin, clopidogrel or both; peptic ulcer in the previous 6 months; thrombocytopenia (platelet concentration lower than 50×10^9 per L); major bleeding (according to the thrombolysis in myocardial infarction [TIMI] criteria) in the past 12 months and pregnancy. 573 patients were enrolled and randomized to receive either double therapy (OAC + clopidogrel, 284 patients) or triple therapy (OAC + clopidogrel and aspirin, 289 patients). The primary endpoint was the occurrence of any bleeding episode during 1-year follow-up. Each bleeding event was classified according to the TIMI criteria, the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) criteria and the Bleeding Academic Research Consortium (BARC) criteria. The secondary endpoint was a composite of death, myocardial infarction, stroke, target-vessel revascularization and stent thrombosis. In the double-therapy group the primary outcome occurred in 54 (19.4 %) patients, while in the triple-therapy group occurred in 126 (44.4 %) patients (hazard ratio [HR] 0.36, 95 % CI 0.26–0.50, $p < 0.0001$). The combined secondary endpoint was observed in 31 (11.1 %) patients in the double-therapy group and in 50 (17.6 %) in the triple-therapy group (HR 0.60, 95 % CI 0.38–0.94, $p = 0.025$).

Strengths of the study

- It deals with a clinically relevant problem. The indication for a coronary stent implantation is common in patients already taking OAC.

Weaknesses of the study

- The study was designed to assess the superiority of double therapy as compared to triple therapy in reducing the incidence of bleeding events. However, the higher bleeding risk for patients taking triple therapy is self-evident and already known [6]. It is more relevant to consider the net clinical benefit taking into account both thrombotic and hemorrhagic events.
- The conclusions reported in the abstract are quite different from those in the article. Reading only the abstract it seems that dual therapy is associated with no increase in the rate of thrombotic events, but the design of the trial does not allow this conclusion.

Question marks

- We wonder if it was methodologically correct to calculate the sample size on the results of previous studies that had considered only major bleedings, while in the present study any type of bleeding was taken into account. Indeed the sample size was calculated to detect a 1-year reduction in bleeding events from 12 to 5 %. However, the incidence of the primary outcome in the study was much greater (44 %).
- Age between 18 and 80 years was one of the inclusion criteria. We wonder why the authors decided to strictly apply this upper age limit; would not have been more appropriate to include also patients older than 80 but eligible for a coronary stent implantation even though on a concomitant OAC therapy?
- We observed that there were more patients already taking aspirin or clopidogrel in the triple-therapy group. We wonder if these patients could have had a higher initial risk. This may explain the difference in the incidence of the secondary endpoint and the general trend of more thrombotic events in the triple-therapy group.

Sponsorship

The study was supported by a private sponsor. The sponsor had no role in study design, data collection and analysis or writing of the report.

Clinical bottomline

The results of this study confirm that in patients with a chronic anticoagulation therapy and an indication to a coronary stent implantation, double anti-thrombotic therapy is associated with a reduced bleeding risk as compared to triple therapy. However, evidence that thrombotic events are not increased with double therapy is still missing. It seems reasonable to keep applying the actual guidelines recommendations for patients already taking OAC therapy, prescribing triple therapy for as short a period as possible, and implanting a bare-metal stent.

Conflict of interest None.

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