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REVIEW

# Antithrombotic management of patients on oral anticoagulation undergoing coronary artery stenting

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## Abstract

Patients on oral anticoagulation (OAC), who are referred for coronary artery stenting account for about 5% of the whole population undergoing percutaneous coronary intervention (PCI). Although relatively small, this patient subset poses particular problems owing to the need to balance carefully the risk of bleeding against the risk of stent thrombosis and thromboembolism. Triple therapy (TT) of OAC, aspirin and clopidogrel appears as the most effective for prevention of stent thrombosis and thromboembolism. However, an increased incidence of major bleeding is to be expected during follow-up. Therefore, TT should be prolonged for as short a time as possible, and implantation of drug-eluting stents avoided. Frequent monitoring of international normalized ratio is also warranted, and the intensity of OAC should be targeted at the lower limit of the therapeutic range. Gastric protection should also be considered for all patients on medium- to long-term TT, owing to the observed highest incidence of bleeding at the gastrointestinal site. Peri-procedural management is cumbersome, and a substantial incidence of in-hospital major bleeding has been reported. Since this latter is more related to procedural variables than to TT itself, choice of radial access, avoidance of glycoprotein Ⅱb/Ⅲa inhibitors, and preference for not interrupting effective OAC should be implemented. However, the evidence on which the recommendations for managing this patient subset are based is limited and of relative poor quality. While waiting for the results of ongoing, large prospective studies that are aimed at conclusively determining optimal medium- to long-term antithrombotic treatment, the official recommendations issued by the Working Group on Thrombosis of the European Society of Cardiology on the management of patients on OAC undergoing PCI with stenting should followed.



**Key words:** Anticoagulants; Warfarin; Aspirin; Clopidogrel; Stents; Percutaneous coronary intervention

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## INTRODUCTION

Patients on oral anticoagulation (OAC), who are referred

for percutaneous coronary intervention with stent implantation (PCI-S) account for about 5% of the whole population undergoing PCI[1-4]. Although relatively small, this patient subset is difficult to manage owing to the need to balance carefully the risk of bleeding against the risk of stent thrombosis and thromboembolism. The higher efficacy and safety of dual antiplatelet treatment (DAT) with aspirin and clopidogrel as compared to OAC after PCI-S has long been demonstrated[5], as well as the superiority of OAC to DAT for conditions such as atrial fibrillation, prosthetic heart valve, or recent venous thromboembolism, for which OAC is indicated[6,7]. Consistently, triple therapy (TT) of OAC, aspirin and clopidogrel appears as the optimal antithrombotic treatment following PCI-S in patients on OAC[8].

## SUMMARY OF THE EVIDENCE AND CURRENT RECOMMENDATIONS

The evidence on which the recommendations for how to manage patients on OAC undergoing PCI-S are based is limited and of relative poor quality. The first studies that have focused on this specific patient subset, which has been previously excluded from clinical trials, appeared only in 2004[9-11]. Over the ensuing years, several contributions were published, and in 2008, the first consensus paper by a dedicated international working group that aimed at summarizing the evidence and giving practical information for the clinician was produced[12]. In summary, TT is the most effective (i.e. the least incidence of stent thrombosis and stroke) compared to other antithrombotic combinations, although a higher incidence of major bleeding, which increases as the treatment prolongs, is to be expected during follow-up[12]. Overall, these results have been confirmed by subsequent work[3,13,14], and represented the base on which the first consensus document of an official Cardiology Society was built[8]. According to this document, patients with atrial fibrillation (and probably also with other indications for OAC), who present with an acute coronary syndrome and/or who are undergoing PCI-S, should receive TT. Owing to the inherent risk of major bleeding, TT should be prolonged for as short a time as possible, and therefore the implantation of drug-eluting stents should be avoided. Whenever a drug-eluting stent is chosen in the light of a higher than expected benefit compared to bare metal stents, such as in long lesions, small vessels and diabetes, TT should be limited to the minimum, that is, 3 mo for a sirolimus, everolimus or tacrolimus-eluting stent and 6 mo for a paclitaxel-eluting stent. A longer duration, however, may be considered in selected patients with a low bleeding risk. In patients who are receiving a bare metal stent in the context of elective PCI-S, TT should be maintained for 1 mo, while a prolongation to 3-6 mo should be considered after an acute coronary syndrome. In order to limit the substantial incidence of peri-procedural/in-hospital bleeding, the radial approach is preferred for PCI-S, glycoprotein Ⅱb/Ⅲa inhibitors should not be administered, and OAC should not be interrupted and bridged with heparin. Also, the intra-procedural dose of heparin should be adjusted to achieve an activated clotting time at the lower limit of the therapeutic range. During medium- to long-term treatment with TT, frequent (i.e. every 1-2 wk) monitoring of international normalized ratio (INR) is warranted and the intensity of OAC targeted at the lower limit of the therapeutic range (i.e. INR 2.0-2.5). Finally, gastric protection should be considered for all patients who receive medium- to long-term TT, because of the observed high incidence of bleeding at the gastrointestinal site. Proton-pump inhibitors, H2-receptor blockers or antacids can be used for that purpose, since the initial association of a negative interference of proton-pump inhibitors on the clinical efficacy of clopidogrel[15] has been recently disproven by the analysis of two large, randomized trials[16].

## IS EVERYTHING CLEAR?

Although derived from the best of contemporary knowledge, the current recommendations appear to be essentially based on sound common sense rather than on objective data. The strength of available evidence in fact is heavily hampered by the limitations of most of the literature.

Most of the initial studies had a retrospective design, were carried out in a single institution, and were of limited size[12]. The few prospective and large datasets actually represent a *post hoc* analysis of trials designed and conducted for other purposes, such as the CRUSADE, GRACE and BASKET trials[3,17,18]. Also, in most cases, outcome comparisons are carried out between patients on TT against contemporary populations treated with DAT with no indication for OAC, rather than within individual populations with indications for OAC, who are receiving different antithrombotic regimens[12]. The true incidence of bleeding associated with TT during follow-up is difficult to evaluate. This is because it is only in a minority of studies that the occurrence of in-hospital bleeding, which is more likely related to procedural variables, such as vascular access site, and use and dose of heparin or glycoprotein Ⅱb/Ⅲa inhibitors, rather than to TT itself, is reported separately, and because the antithrombotic treatment that is actually ongoing at the time of an event is documented only rarely. As it has been argued, it is unclear at present what is responsible for bleeding in patients on TT[19,20], since hemorrhagic complications that occur weeks or months after treatment has been completed cannot plausibly be attributed to this regimen, even though the analysis is carried out according to the initially assigned treatment. The INR value at the time of bleeding is only rarely reported, while an over-therapeutic level might account in itself for a hemorrhagic complication, independently from the combined administration of antiplatelet agents. Finally, no valuable information is available on the concomitant use of gastric protection, which could actually be useful in limiting the incidence of bleeding in a population

like that which is receiving TT, in which hemorrhage has been shown to occur mostly at gastrointestinal sites.

Most recent work has focused on some specific aspects of the issue. The feasibility and safety of the radial approach during uninterrupted OAC has been prospectively evaluated in 50 patients at a single institution in France[21]. At 1 mo follow-up, no thrombotic events or major bleeding were observed[21]. In a Finnish multicenter database that included 377 atrial fibrillation patients on OAC who were undergoing PCI-S, the safety of glycoprotein Ⅱb/Ⅲa administration was retrospectively evaluated[22]. A sixfold increase in major bleeding was found in patients treated with glycoprotein Ⅱb/Ⅲa inhibitors compared to those not receiving these agents[22]. The in-hospital adverse cardiovascular event and bleeding rates were prospectively examined in 163 patients with an indication for OAC, who were enrolled in several centers in Italy and Spain[2]. The overall major bleeding rate was about 4%, with the radial and femoral approach being of borderline significance as predictors of decreased and increased incidence of bleeding, respectively[2].

When trying to determine the true hemorrhagic rate associated with medium- to long-term TT, the figure of about 4%, which is consistent with that observed in larger datasets[3,14,17], should be subtracted from the 5%-10% occurrence of major bleeding reported for these patients after ≥ 12 mo follow-up[8,12]. The remaining 1%-6% bleeding rate for medium- to long-term TT may actually be closer to the reality. Indeed, in a prospective randomized study of 515 patients on OAC, who were assigned to TT or DAT after PCI-S at a single center in Germany, the occurrence of major bleeding was as low as about 1.5%, and did not differ in the two groups[23]. However, this is in contrast with the results of a recent large retrospective study in Spain of 604 atrial fibrillation patients undergoing PCI-S, in which the use of drug-eluting stents, and therefore of prolonged TT, was associated with an increased incidence of major bleeding over 4 years follow-up[13]. It also contrasts with a recent retrospective analysis of 813 patients enrolled in the Swiss BASKET trial, in which patients on TT had a significantly higher incidence of major bleeding compared to those with DAT at 3 years, while no difference was present at discharge[3]. Once again, however, some major flaws must be acknowledged. In the Spanish study, only 50% of patients that received a drug-eluting stent were discharged on TT, with no information as to whether subsequent bleeding occurred in this subset or in others treated with different antithrombotic regimens[13]. Also, the duration of TT and whether it was ongoing at the time of bleeding was not reported[13]. Out of the patients who experienced late major bleeding in the BASKET trial, only half of them were on TT, whereas the remaining half were receiving the combination of OAC and aspirin[3]. Again, little information is given on the INR level at the time of the hemorrhagic complications[3]. In patients on TT, successful maintenance of the INR level between 2.0 and 2.5 has been shown prospectively to be associated with bleeding that is comparable to that in patients on DAT, while deviations above this level carry a definite increased risk of bleeding complications[1].

## CONCLUSION

The peri-procedural management of patients on OAC undergoing PCI-S is well substantiated by available evidence, and measures, such as choice of radial access, avoidance of glycoprotein Ⅱb/Ⅲa inhibitors, and preference for maintaining effective OAC with additional low doses of extra anticoagulants throughout the procedure, should definitively be implemented to limit the risk of major in-hospital bleeding. Owing to the well-recognized unfavorable prognostic role of bleeding and/or transfusion in patients with acute coronary syndromes[24], meticulous attention to the above-mentioned technical and pharmacological aspects of PCI-S should be applied even more to patients at high risk of bleeding, such as those on OAC. More uncertain at present is the true risk of hemorrhagic complications associated with prolonged administration of TT. Since the occurrence of even minor bleeding has been shown to prompt the interruption of one or both antiplatelet agents[25], which in turn is the major responsible factor for stent thrombosis[26], it is mandatory to keep this risk as low as possible. Therefore, avoidance of drug-eluting stent implantation, careful maintenance of the INR level at the lower side of the therapeutic range, and extensive use of gastric protection should be applied during prolonged TT, which certainly represents the optimal antithrombotic treatment for OAC patients undergoing PCI-S. Large prospective studies are currently ongoing[27-30] with the aim of conclusively defining the safety of prolonged TT and the safety and efficacy of combination of OAC and clopidogrel. This latter regimen has been proposed as an alternative to TT for patients at high risk of bleeding, especially after completion of an initial short period of TT[8,12]. However, further data are needed before the combination of OAC and clopidogrel may be considered, since the initial evidence supporting comparable efficacy[31] has been recently counterbalanced by the observation in a very large nationwide study of a safety profile no better than that of TT[4].

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