THE WOEST STUDY: IS NOW THE TIME TO UPDATE THE RECOMMENDATIONS REGARDING THE ANTITHROMBOTIC THERAPY IN PATIENTS WITH INDICATION FOR ORAL ANTICOAGULATION UNDERGOING CORONARY STENT IMPLANTATION?

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Disclosure: No potential conflict of interest.
Citation: EMJ Int Cardiol. 2013;1:59-62.

ABSTRACT

Triple therapy (TT) of warfarin, aspirin, and clopidogrel is currently recommended as the antithrombotic therapy for patients with an indication for oral anticoagulation (OAC) undergoing percutaneous coronary intervention (PCI) with stent implantation (PCI). While appearing to be the most effective regimen in preventing the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis, TT is however associated with an increased incidence of bleeding. In the recent 'What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing' (WOEST) study, dual therapy (DT) with warfarin and clopidogrel has been shown to be significantly safer than TT on the occurrence of total bleeding, with no decrease in efficacy, as the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis was also significantly lower. Owing to the limited effect of DT on the occurrence of clinically major bleeding, as well as to the large undersizing of the WOEST study for a reliable evaluation of the effect on adverse cardiac events, and especially stent thrombosis, the results of the WOEST study should not yet prompt the substitution of TT for DT as the antithrombotic regimen for patients with an indication for OAC who are submitted to PCI.

Keywords: Percutaneous coronary intervention, stent, warfarin, oral anticoagulation.

INTRODUCTION

Triple therapy (TT) of warfarin, aspirin, and clopidogrel is currently recommended in patients with an indication for oral anticoagulation (OAC), because of atrial fibrillation, venous thromboembolism, and mechanical heart valve, who undergo percutaneous coronary intervention (PCI) with stent implantation.[1-3] While acknowledging that it is generally derived from studies of suboptimal quality (i.e. single-centre, retrospective, and small size), such recommendation is based upon the observation of a general superior efficacy of TT on the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis.[1-3] Such superior efficacy however, is accompanied by lower safety, that is increased incidence of bleeding.[1-3]

Because of the established negative prognostic impact of bleeding in patients with acute coronary syndrome and/or submitted to PCI,[4] the identification of an antithrombotic regimen with a better risk/benefit ratio has long been advocated. The 'What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing' (WOEST) study,[5] where 573 patients with an indication for OAC and submitted to PCI where (open-label) randomised to TT or dual antithrombotic therapy of warfarin and clopidogrel (DT), appears to have achieved such result. At

12-month follow-up in fact, the safety of DT has been significantly higher than TT (64% relative reduction of the incidence of total bleeding), in the absence of any decrease in efficacy, which in contrast was also significantly superior in the DT compared to the TT group (40% relative reduction of the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis).[5]

From the results of the WOEST study[5] an important and urgent question arises: is it possible and indicated today, to recommend DT instead of TT as antithrombotic regimen in patients with indication for OAC undergoing PCI?

CONSIDERATIONS ON SAFETY

Primary End-Point

While, on the one hand, the higher safety of DT compared to TT cannot be ignored, on the other hand it should not be overlooked that the difference between the two groups is mostly driven by a decrease in the incidence of the bleeding events of less clinical importance (that is, either Thrombolysis in Myocardial Infarction (TIMI) minimal and minor, Global Utilisation of Streptokinase and Tissue Plaminogen Activator for Occluded Coronary Arteries (GUSTO) mild and moderate, and BARC 1, 2 and 3a), in the absence of significant differences in the incidence of bleeding of higher clinical relevance (that is, TIMI major, GUSTO severe, and BARC 3b and 3c) (Table 1). And even if the former may have a negative prognostic impact (though generally indirect, and due to an increase in ischemic events related to the withdrawal of antithrombotic therapies in response to bleeding), it is the latter to impact more and directly on the patient prognosis, owing to the location (e.g. intracranial, intra-ocular, intra-pericardial) and/or the associated hemodynamic impairment (e.g. shock, hypotension with associated ischemia).[4] The lower incidence of GUSTO moderate (statistically significant) and BARC 3a (of borderline statistical significance) bleeding observed in the DT group in turn, may be largely dependent on the significantly lower rate of blood transfusions (61% reduction),[5] as they represent a classification criterion for those types of bleeding (Table 1). Despite the existence of recommendations aiming to standardise the use of blood transfusions,[6] the wide variability and complexity of the individual clinical contexts (e.g. comorbidities, haemodynamic impairment) may make the use of blood transfusions extremely inhomogeneous,[7] at the point to question the actual validity of blood transfusions rate as an end-point in clinical trials.

With regards to the course of the Kaplan-Meier curves relative to the incidence of total bleeding, it is of note that they diverge immediately, continue to diverge during the first 30 days, and then proceed almost parallel up to the end of follow-up.[5] Such behaviour suggests that the lower safety of TT is less

Not significant:	TIMI major	Intracranial; decrease of haemoglobin ≥5 g/dl or haematocrit ≥15%
	GUSTO severe	Intracranial; leading to haemodynamic compromise
	BARC 3c	Intracranial; intra-ocular with vision impairment
	BARC 3b	Decrease of haemoglobin ≥5 g/dl; cardiac tamponade; requiring surgical intervention or inotropic support
	BARC 3a*	Decrease of haemoglobin 3-5 g/dl; causing blood transfusion
Significant:	TIMI minimal	Decrease of haemoglobin <3 g/dl or haematocrit <9%
	TIMI minor	Decrease of haemoglobin ≥3 g/dl or haematocrit ≥10%; decrease of haemoglobin ≥4 g/dl or haematocrit ≥12% with no overt bleeding
	GUSTO moderate	Causing blood transfusion without haemodynamic compromise
	GUSTO mild	Not satisfying moderate or severe criteria
	BARC 2	Requiring non-surgical medical intervention; leading to hospitalisation or increased level of care; prompting evaluation
	BARC 1	Not actionable and not requiring unscheduled studies, hospitalisation or treatment

* p=0.054 DT = double therapy; TT = triple therapy; TIMI = Thrombolysis In Myocardial Infarction; GUSTO = Global Utilisation of Streptokinase and Tissue Plaminogen Activator for Occluded Coronary Arteries; BARC = Bleeding Academic Research Consortium.

Table 1. Differences in the incidence of bleeding in DT and TT groups (primary end-point).

attributable to a prolonged exposure to such regimen, and more dependent on early variables (e.g. peri-PCI). Indeed, the limited use of the radial approach (about 25%), as well as of the continuation of OAC throughout PCI (about 40%), albeit not different in the two groups,[5] may have contributed to the higher incidence of bleeding in the group receiving a more aggressive antithrombotic treatment, TT. In OAC patients undergoing PCI, the femoral approach and the periprocedural interruption of OAC have been associated with an increased incidence of major bleeding and access site complications.[8] In the TT group of the WOEST study,[5] a relevant proportion (i.e. 7%) of higher clinically relevant bleeding occurred at the vascular access site.[5]

It is finally of note that the incidence of total bleeding (primary safety end-point) was three to four-fold higher than both reported in the literature[9,10] and planned at the time of sizing the study (44.4% vs. 12% in the TT group, and 19.4% vs. 5% in the DT group).[5] While, on the one hand, being in contrast with the exclusion from the enrolment of those patients at highest bleeding risk, such as those with previous intracranial bleeding and TIMI major bleeding during the previous 12 months,[5] on the other hand the explanation given by the authors, that is the tracking of all bleeding events (and not only major), and the prolonged use of clopidogrel associated with the preponderant use of drug-eluting stent (in about two-thirds of cases), appears hardly acceptable. In a prospective, observational study enrolling 622 atrial fibrillation patients undergoing PCI with drug-eluting stents in all cases, the 12-month incidence of total bleeding in the TT and DT (comprising however the combination of warfarin with either aspirin or clopidogrel) was approximately 12% and 7%, respectively.[9] Even though it is not possible to determine whether the excessive incidence of bleeding in the WOEST study, and especially in the TT[5] may have impacted on the results, it remains uncertain whether the same outcomes are to be expected also in the real-world populations of daily clinical practice.

CONSIDERATIONS ON EFFICACY

Secondary End-Point

The significant higher efficacy of DT compared to TT on the combined incidence of stroke, death, myocardial infarction, re-revascularisation, and stent thrombosis is difficult to interpret. While a reduction, albeit not statistically significant, of the majority of individual components of the combined efficacy end-point is apparent, the global effect appears mostly driven by the reduction (by 61%) in total mortality.[5] In turn, the decrease in total mortality is largely driven by the reduction, however of borderline statistical significance (p=0.069), of non-cardiac mortality, with no significant difference on cardiac mortality.[5] In the absence of a plausible pathophysiological mechanism to explain an effect on non-cardiac mortality of antithrombotic drugs, which acts by preventing adverse vascular events, it cannot be excluded that the results on mortality observed in the WOEST study[5] may only be a play of chance. It should not be overlooked however that the study was not sized to identify differences in the efficacy of DT compared to TT. If it is right, and proper, consider this when trying to interpret the results regarding the secondary efficacy end-point and mortality, even more so when trying to examine the incidence of stent thrombosis. Despite the fact the omission of aspirin in the DT group was not associated with an increase in stent thrombosis (for the prevention of which the pharmacological standard is currently represented by the combination of aspirin and clopidogrel, or another $P2Y_{12}$ receptor inhibitor), the WOEST study[5] does not actually allow any solid conclusion in this regard. The commonly reported yearly incidence of stent thrombosis (about 1-2%)[11] would have requested a much larger population size. This is even more true when considering that the WOEST population was at quite low risk of stent thrombosis, due to the low prevalence (25-30%) as indication for PCI of acute coronary syndrome, which is an established predictor of stent thrombosis.[11]

CONCLUSIONS

Based on the considerations above, it can be concluded that the WOEST study,[5] which must be regarded as the only prospective, randomised study carried out so far on this topic, essentially confirms previous observations of a general higher safety of DT compared to TT.[12] Again in accordance with previous observations,[9,10] the higher safety is largely attributable to a reduced incidence of minor rather than major bleeding. The WOEST study[5] does not provide usable information regarding the efficacy of DT on the incidence of adverse cardiac events, including death, myocardial infarction, re-revascularisation, and especially stent thrombosis. In this regard, it should also not be overlooked that because of the phenomenon of clopidogrel 'resistance' (which may involve up to 30% of patients, and is associated with an increased risk of adverse cardiac events),[13] a relevant proportion

of patients receiving DT may actually be exposed to the action of warfarin only. And the insufficient efficacy of warfarin monotherapy in preventing the adverse cardiac events after PCI has long been demonstrated.[14]

Therefore, as a whole, the results of the WOEST study[5] do not support the general use of DT in place of TT as an antithrombotic treatment for patients with an indication for OAC undergoing PCI. The uncertainty regarding the real efficacy of DT for the prevention of adverse cardiac events, and especially stent thrombosis, also precludes its use in selected patients, such as those at increased haemorrhagic risk.

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