



## Přehledový článek | Review article

## The WOEST study: Critical considerations and applicability

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## SOUHRN

Léčba trojkombinací (triple therapy – TT) antagonistů vitamínu K (VKA), kyselinou acetylsalicylovou a clopidogrelem je v současné době doporučována jako optimální antitrombotická terapie u pacientů s nutnou perorální antikoagulací během perkutánní koronární intervence spolu s implantací stentu (PCI-S). I když je TT zřejmě vysoce účinná v prevenci kombinované incidence úmrtí, infarktu myokardu, opakované revaskularizace, trombózy stentu a cévní mozkové příhody, je zároveň spojena s vysokou incidencí krvácení. Nedávno publikovaná studie WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) prokázala, že duální terapie (DT) s warfarinem a clopidogrelem je statisticky významně bezpečnější než TT z hlediska celkové incidence krvácení bez zjevného snížení účinnosti, protože kombinovaná incidence úmrtí, infarktu myokardu, opakované revaskularizace, trombózy stentu a cévní mozkové příhody byla v rameni DT ve skutečnosti rovněž nižší než v rameni TT. Vzhledem k nedostatečné statistické síle studie WOEST pro spolehlivé zhodnocení parametrů účinnosti, zvláště v případě trombózy stentu, a vzhledem k omezené vyšší bezpečnosti DT oproti TT v případě klinicky významného krvácení se domníváme, že výsledky studie WOEST by neměly vést k uáhlenému přijetí DT jako antitrombotického režimu volby u pacientů indikovaných k podání VKA při plánované PCI-S.

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## ABSTRACT

Triple therapy (TT) with a vitamin K-antagonist (VKA), aspirin, and clopidogrel is currently recommended as the optimal antithrombotic therapy for patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention with stent implantation (PCI-S). While appearing highly effective for preventing the combined incidence of death, myocardial infarction, repeat revascularization, stent thrombosis, and stroke, TT is associated with a high 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 apparent reduction in efficacy, as the combined incidence of death, myocardial infarction, repeat revascularization, stent thrombosis, and stroke was actually also significantly lower in the DT than in the TT arm. Because of the underpowered size of the WOEST study for a reliable evaluation of the efficacy outcomes, especially stent thrombosis, and because of the limited superior safety of DT vs TT for the occurrence of clinically major bleeding, we maintain that the results of the WOEST study should not precipitously lead to the adoption of DT as the antithrombotic regimen of choice for patients with an indication for VKA who are submitted to PCI-S.

## Keywords:

Antiplatelet therapy

Oral anticoagulation

Percutaneous coronary intervention

Stent

Stent thrombosis

Triple therapy

Vitamin K-antagonists

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## Introduction

Triple therapy (TT) with a vitamin K-antagonist (VKA), aspirin, and clopidogrel is currently recommended as the optimal antithrombotic therapy for patients on oral anticoagulation (OAC) because of atrial fibrillation, a mechanical heart valve, or other conditions, undergoing percutaneous coronary intervention with stent implantation (PCI-S) [1,2]. While appearing effective in preventing the combined incidence of death, myocardial infarction, repeat revascularization, stent thrombosis, and stroke, TT is associated with a high incidence of bleeding [1,2]. Because of the established negative impact of bleeding on the prognosis of patients undergoing PCI-S [3], safer antithrombotic regimens in such occurrences have long been awaited, provided they are not less effective.

The recent *What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing* (WOEST) study [4] has shown not only that dual therapy of VKA and clopidogrel (DT) is indeed safer, but is also apparently more effective, than TT (Table 1). Thus, should now DT be adopted in clinical practice in patients requiring oral anticoagulation and undergoing PCI-S?

To try to answer this question, we will critically review the design and results of the WOEST study and discuss its implications [4].

## WOEST study design

The prospective, multicenter, randomized design is a major strength of the WOEST study [4], making it the only prospective randomized trial carried out so far on OAC patients submitted to PCI-S, and fulfilling most of the formal requirements for optimal clinical research. Randomization in fact, gives each participant in the study equal chances of being assigned to any treatment group, limiting systematic bias; tends to generate comparable treatment groups; and maximizes chances that differences in end points occurring during the trial are solely due to treatment, thus certainly being the best way to determine which of any compared treatments is best.

On the other hand, the open-label design of the WOEST study [4] weakens the strength of the results, as it may carry methodological problems. These include: (a) the possible exclusion from randomization of patients considered to be at increased risk of stent thrombosis; (b) over- or under-reporting the outcome measures by participants; and (c) physicians' influence on the reporting of outcome measures. Indeed, patients enrolled in the WOEST study [4] are younger than those generally encountered in real-world unselected populations (mean age about 70 years vs about 73–74 years) [5–7]; and the incidence of total bleeding is 3-to-4-fold higher than the average incidences reported in the literature [7,8], and also much higher than the in-

**Table 1 – Safety and efficacy outcomes in the WOEST study [4]**

	Dual therapy (n = 279)	Triple therapy (n = 284)	Hazard ratio (95% CI)	p value
Total bleeding	54 (19.4%)	126 (44.4%)	0.36 (0.26–0.50)	< 0.0001
Death, MI, stroke, TVR, stent thrombosis	31 (11.1%)	50 (17.6%)	0.60 (0.38–0.94)	0.025

MI – myocardial infarction; TVR – target vessel revascularization.

**Table 2 – Differences in the incidence of bleeding in the Dual Therapy and Triple Therapy groups of the WOEST study [4]**

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

\*  $p = 0.054$

BARC – Bleeding Academic Research Consortium; GUSTO – Global Utilization of Streptokinase and Tissue plasminogen activator for Occluded coronary arteries; TIMI – Thrombolysis In Myocardial Infarction.

cidence anticipated at the time of sample size calculation (44.4% vs 12% in the TT group, and 19.4% vs 5% in the DT group) [4]. While it is unclear whether such a finding may have impacted on the results, the explanation of such high bleeding rate given by the authors is unsatisfactory [4]. In fact, in another prospective, observational study enrolling 622 atrial fibrillation patients undergoing PCI-S with drug-eluting stents in all cases, and which tracked all bleeds – not only major bleeds – and also tended to prolong the use of clopidogrel because of the systematic use of drug-eluting stents, the incidences of total bleeding at a 12-months were approximately 12% and 7% in the TT and DT groups (in the latter case comprising warfarin with either aspirin or clopidogrel), respectively [7], which are about one third of what reported in the WOEST study [4].

The main methodological limitation of the WOEST study [4] is, however, the small sample size, including only 573 patients overall. Such sample size provides sufficient power only to detect differences in the incidence of total bleeding, which was indeed the primary outcome (a safety outcome) of the study. No reliably significant detection of differences in the secondary (efficacy) outcome, including cardiovascular death, myocardial infarction, target vessel revascularization, stent thrombosis, and stroke, nor – even more – of its individual components could be done with such numbers, due to their rarer occurrence.

## WOEST study results

### Safety

In the WOEST study bleeding episodes were seen in 54 (19.4%) patients receiving DT and in 126 (44.4%) receiving TT (hazard ratio [HR] 0.36, 95% CI 0.26–0.50,  $p < 0.0001$ ). In the DT group, six (2.2%) patients had multiple bleeding events, compared with 34 (12.0%) in the TT group. Eleven (3.9%) patients receiving DT required at least one blood transfusion, compared with 27 (9.5%) patients in the TT group (odds ratio from Kaplan-Meier curve 0.39, 95% CI 0.17–0.84,  $p = 0.011$ ). Although evident – but also qualitatively expected – the superior safety of DT vs TT in the trial, when closely inspected, was mostly driven by a decrease in the incidence of bleeding events of lesser clinical relevance (TIMI minimal/minor bleeding, GUSTO mild/moderate bleeding, and BARC 1/2/3a bleeding), in the absence of significant differences in the incidence of bleeding of higher clinical relevance (TIMI major bleeding, GUSTO severe bleeding, and BARC 3b/3c bleeding) (Table 2) [4]. While less clinically important bleeding events, such as TIMI minimal/minor, GUSTO mild/moderate, and BARC 1/2/3a bleeds (Table 2) [4], are known to have some negative prognostic impact (largely indirect, due to an increase in ischemic events related to the withdrawal of antithrombotic therapies in response to bleeding), bleeding events of higher clinical relevance, such as TIMI major, GUSTO severe, and BARC 3b/3c (Table 2), clearly impact more and more directly on patients' prognosis [3]. Of note, the reported lower incidence of GUSTO moderate (statistically significant) and BARC 3a (of borderline statistical significance) bleeding observed in the DT group was also likely affected by the significantly lower rate of blood transfusions [4], as they represent a classification criterion for those types of bleeding (Table 2). The use of blood transfusions,

despite the existence of recommendations to standardize their use [9], remains on the one hand extremely subjective, and on the other hand extremely variable [10], depending on the complexity of the clinical contexts (comorbidities, hemodynamic impairment), and possibly also here affected by the knowledge of the therapy given to individual patients due to the open-label design.

In addition to this, the Kaplan-Meier curves relative to the incidence of total bleeding appear to diverge immediately and continue to diverge during the first 30 days after randomization, but then remain almost parallel up to the end of follow-up in the WOEST study [4], making the lesser safety of TT vs DT less attributable to the prolonged exposure to such a regimen, and, conversely, more dependent on early (peri-PCI-S) variables. Indeed, the limited use of the radial approach (about 25%), as well as of the continuation of VKA throughout PCI in about 40% of patients, albeit not different in the two groups [4], may have contributed to the higher incidence of bleeding in the TT group, receiving a more aggressive antithrombotic treatment.

Because of these considerations, the still expected difference in bleeding between the two therapeutic regimens investigated is less impressive than at first sight.

### Efficacy

Regarding the combined incidence of cardiovascular death, myocardial infarction, target vessel revascularization, stent thrombosis, and stroke, the reported significant superiority of DT over TT appears mostly driven by the reduction of total mortality (HR 0.39; 95% CI 0.16–0.93;  $p = 0.027$ ), although a numerical, not statistically significant, lower incidence of most the individual components of the combined efficacy end point is to be acknowledged [4]. The lower total mortality in turn appears to be largely driven by the lower incidence (close to statistical significance: HR 0.36; 95% CI 0.11–1.13;  $p = 0.069$ ), of non-cardiac mortality, with no significant difference in cardiac mortality (HR 0.43; 95% CI 0.11–1.66;  $p = 0.207$ ) [4]. In the absence of a plausible pathophysiological explanation for an effect of antithrombotic drugs, which should only act by preventing thrombotic vascular occlusion, on non-cardiac mortality, such an apparent striking result on mortality is possibly due to the play of chance.

Despite being properly acknowledged by the authors themselves [4], this limitation is even more relevant when examining differences in the rare outcome of stent thrombosis, which is the primary rationale for the combination of aspirin and a P2Y<sub>12</sub>-receptor inhibitor such as clopidogrel in other post-PCI-S settings. In WOEST the omission of aspirin in the DT group was not apparently associated with an increased rate of stent thrombosis [4]. Since the commonly reported incidence of stent thrombosis is extremely low (about 1–2%/year) [11], the absence of a significant difference in such an outcome is not a proof of equal efficacy of the two treatments because of the high likelihood of a type II error (detecting such a difference or proving non-inferiority would have required for both a much larger population).

## Conclusions and practical considerations

The WOEST study essentially confirms, albeit in a prospective, randomized fashion, previous observations of a better

safety of DT compared to TT in patients on VKA undergoing PCI-S [7,12,13] and/or receiving combined antithrombotic therapies [12,13]. The magnitude of benefit on the incidence of total bleeding with DT compared to TT (about 50–60% in WOEST) is similar to that observed in large, nationwide, Danish databases [4,12,13]. In such databases, however, the number needed to harm was nearly the same with TT and DT (12.5 and 15.2, respectively) [12]. Also in accordance with previous observations [7,8], in the WOEST study [4] the higher safety is largely attributable to a reduced incidence of minor – rather than major – bleeding.

Regarding efficacy, the WOEST study [4], largely because of its size, does not provide definitive information on the efficacy of DT vs TT on the incidence of adverse cardiac events, including death, myocardial infarction, repeat revascularization, and especially stent thrombosis. A further caution in transferring these results to clinical practice is the consideration that, because of the reported inadequate clopidogrel responsiveness occurring in up to 30% of patients and associated with an increased risk of adverse cardiac events [14], such a relevant proportion of patients receiving DT would actually be exposed to the action of VKA only, an antithrombotic regimen which has long been demonstrated to have insufficient efficacy in preventing adverse cardiac events after PCI-S [15].

As a whole therefore, the results of WOEST [4] do not warrant the unrestricted adoption of DT in place of TT as an antithrombotic treatment for VKA patients undergoing PCI-S. We acknowledge that further data derived from large, nationwide, Danish registries have more recently reported comparable efficacy of DT and TT [16]), but such data do not derive from a prospective randomized trial and are therefore highly likely to suffer from selection biases. At the moment, only highly selected patients at very high risk of bleeding and with a concomitant low risk of stent thrombosis, such as those undergoing PCI-S for stable coronary artery disease (two-thirds of patients enrolled in the WOEST study [4]), but also with large stent diameter and short length stents implanted, and of young age, might at present be considered candidate for DT. In general, the WOEST study awaits confirmation from larger prospective randomized trials. Whether and how DT will retain a place in the upcoming therapeutic scenario, including new direct oral anticoagulants (dabigatran, rivaroxaban, apixaban), and new antiplatelet agents (prasugrel, ticagrelor), also remain to be investigated.

#### Conflict of interest

None.

#### Funding body

None.

#### Ethical statement

The research here presented was done according to ethical standards.

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