



The risk of bleeding of triple therapy with vitamin K-antagonists, aspirin and clopidogrel after coronary stent implantation: Facts and questions

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Abstract

Background Triple therapy (TT) with vitamin K-antagonists (VKA), aspirin and clopidogrel is the recommended antithrombotic treatment following percutaneous coronary intervention with stent implantation (PCI-S) in patients with an indication for oral anticoagulation. TT is associated with an increased risk of bleeding, but available evidence is flawed by important limitations, including the limited size and the retrospective design of most of the studies, as well as the rare reporting of the incidence of in-hospital bleeding and the treatment which was actually ongoing at the time of bleeding. Since the perceived high bleeding risk of TT may deny patients effective strategies, the determination of the true safety profile of TT is of paramount importance. **Methods** All the 27 published studies where the incidence of bleeding at various time points during follow-up has been reported separately for patients on TT were reviewed, and the weakness of the data was analyzed. **Results** The absolute incidence of major bleeding upon discharge at in-hospital, ≤ 1 month, 6 months, 12 months and ≥ 12 months was: $3.3\% \pm 1.9\%$, $5.1\% \pm 6.7\%$, $8.0\% \pm 5.2\%$, $9.0\% \pm 8.0$, and $6.2\% \pm 7.8\%$, respectively, and not substantially different from that observed in previous studies with prolonged dual antiplatelet treatment with aspirin and clopidogrel. **Conclusions** While waiting for the ongoing, large-scale, registries and clinical trials to clarify the few facts and to answer the many questions regarding the risk of bleeding of TT, this treatment should not be denied to patients with an indication for VKA undergoing PCI-S provided that the proper measures and cautions are implemented.

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Keywords: percutaneous coronary intervention; stent; bleeding; oral anticoagulation; vitamin K antagonists; aspirin; clopidogrel

1 Introduction

Triple therapy (TT) with vitamin K-antagonists (VKA), aspirin and clopidogrel is the recommended antithrombotic treatment following percutaneous coronary intervention with stent implantation (PCI-S) in patients with an indication for oral anticoagulation, such as those with atrial fibrillation at moderate to high thromboembolic risk, mechanical heart valves, previous cardiogenic thromboembolism and recent deep vein thrombosis or pulmonary embolism.^[1–3] Owing to the superior efficacy of VKA compared to dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in preventing thromboembolic and thrombotic complications in patients with atrial fibrillation and mechanical aortic valve,^[4,5] and owing to the superior efficacy of DAPT compared to VKA, with or without aspirin, in preventing

adverse cardiac events following PCI-S,^[6] TT with VKA, aspirin and clopidogrel is regarded as the optimal antithrombotic regimen in patients with an indication for VKA undergoing PCI-S.

Previous studies^[1,2] and recent meta-analyses^[7,8] have indeed shown that TT is associated with the lowest incidence of stroke compared to DAPT or the combination of VKA and a single antiplatelet agent (either aspirin or clopidogrel). Such result, however, appears to come at the price of an increased incidence of bleeding complications during follow-up.^[1,2,7,8] These bleedings are mostly major, and appear to increase in rate as TT prolongs over time.^[1,2] Because of that, TT is often not prescribed to patients in whom it is indicated, and even when prescribed, it is maintained for duration shorter than optimal. In addition, drug-eluting stents are generally not implanted, owing to the need for prolonged clopidogrel, and hence TT, administration. As a consequence of the reported increase in major bleeding complications with prolonged TT, treatments of proven efficacy, such as a 12-month course of clopidogrel after PCI-S for an acute coronary syndrome, regardless of whether a bare-metal or a drug-eluting stent has been implanted, or the implantation of a drug-eluting

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stent in a diabetic patient, especially in the presence of a long lesion in a small vessel, may be denied to patients in whom the highest benefit is anticipated.

As previously pointed out,^[9,10] however, uncertainty still exists over whether the safety profile of TT is really suboptimal. The evidence on which this assumption is based, in fact, is in general of poor quality: most of the studies are retrospective, and the few prospective studies are generally small and by single-center.^[1,10] Furthermore, outcome comparisons were carried out within the same study cohort only in a minority of studies, while in most of them either no comparison or comparison against contemporary populations of patients with no indication for oral anticoagulation undergoing PCI-S and receiving DAPT was performed.^[1,10] Finally, only seldom the occurrence of in-hospital bleedings, which are related more to procedural variables (*i.e.*, vascular access site, use of glycoprotein IIb/IIIa inhibitors, use of heparin bridging strategies after temporary VKA interruption, etc.) than to TT itself, have been reported separately from those occurring after discharge.^[9,10] The international normalized ratio (INR) at the bleeding event has also been rarely reported, as well as the antithrombotic treatment actually ongoing at the time of bleeding, when that initially assigned might have already been changed (*i.e.*, withdrawal of clopidogrel after a due course of several weeks or months).^[9,10]

While waiting for a definitive clarification of the efficacy in preventing thromboembolic and thrombotic complications of TT compared to other regimens, such as the combination of VKA and clopidogrel, it is now of paramount importance to determine the true safety profile of TT.

In this paper, the available studies where data on the bleeding rate in patients treated with TT after PCI-S are separately reported, will be critically reviewed.

2 Methods

Various combinations of key words such as percutaneous coronary intervention, stent, oral anticoagulation, warfarin, antiplatelet agents were used for Medline search. All English language, full-text articles from January 2004 to December 2010 reporting safety outcomes in patients with indication for VKA treatment who underwent PCI-S were selected for this review. References from these publications were also reviewed. Data were abstracted from reported events in full-text articles. A total of 28 studies met the criteria. One study^[11] was excluded owing to subsequent duplicate publication after inclusion of more

patients, leaving therefore 27 studies available for the analysis.^[12–38]

3 Results

Of the 27 studies included in this review, the vast majority had a retrospective, single-center design (52%), while the remaining were either prospective, single-center (15%), prospective, multi-center (15%), prospective, multi-center with the data on TT patients analyzed *post-hoc* (11%), or retrospective, multi-center (7%) (Table 1). The overall number of patients receiving TT in the published studies is 3,791 (Table 1). The indications for VKA are reported in 93% of the studies (Table 1). In five studies (19%), only patients with atrial fibrillation were included (Table 1). In the remaining studies, atrial fibrillation was the most frequent indication for VKA (mean 57%; range: 24%–84%), followed by prosthetic heart valves (mean 9%; range: 0%–25%) and previous stroke (mean: 3%; range: 0%–13%) (Table 1). The indications for PCI-S are reported in 78% of the studies (Table 1). While in one study (4%), ST-elevation myocardial infarction (STEMI) was the only indication for PCI-S, in the remaining the mean prevalence of STEMI, non ST-elevation acute coronary syndromes and stable ischemic heart disease was 24% (range: 3%–57%), 40% (range: 0%–80%), and 36% (range: 0%–85%), respectively (Table 1).

Among the procedural variables which may influence the occurrence of in-hospital bleeding, the use of radial approach, glycoprotein IIb/IIIa inhibitors, and bridging strategies with heparin after temporary VKA withdrawal was reported in 44%, 63% and 22% of studies, respectively (Table 2). Apart from one study (4%) where the radial approach was used in all patients, in the remaining it was used on average in 28% (range: 0%–66%) of cases (Table 2). The mean use of glycoprotein IIb/IIIa inhibitors was 29% (range: 2.5%–61%), while that of heparin bridging strategies in the 96% of the studies where it was not used as the standard approach for all cases, was on average 36% (range: 0%–88%), (Table 2).

The time points at which data on the incidence of major bleeding during follow-up are available include: hospitalization (26% of studies), ≤ 1 month (15%), 6 months (19%), 12 months (41%), and ≥ 12 months (19%) (Table 3). Similarly, minor bleedings were evaluated at ≤ 1 month (19% of studies), 6 months (7%), 12 months (7%), and ≥ 12 months (15%) (Table 3), respectively.

Table 1. Design, size and indications for VKA therapy and PCI-S in the various studies.

Ref.	Year	Design	PTS (n)	TT PTS (n)	Indication for VKA (%)				Indication for PCI-S (%)		
					AF	Mechanical valve	Stroke	Other	STEMI	NSTE-ACS	Other
Orford, <i>et al</i> ^[12]	2004	Retrospective, 1-center	66	66	39	25	6	30	12	28	60
Mattichak, <i>et al</i> ^[13]	2005	Retrospective, 1-center	82	40	43	8	0	49	100	0	0
Khurram, <i>et al</i> ^[14]	2006	Retrospective, 1-center	214	107	80	5	0	15	-	-	-
Konstantino, <i>et al</i> ^[15]	2006	Retrospective, multi-center	2737	76	-	-	-	-	57	41	2
Lip & Karpha ^[16]	2006	Retrospective, 1-center	35	6	100	0	0	0	31	63	6
Porter, <i>et al</i> ^[17]	2006	Retrospective, 1-center	180	180	37	6	5	52	46	37	17
Rubboli, <i>et al</i> ^[18]	2007	Retrospective, 1-center	49	20	60	8	6	26	31	29	40
Nguyen, <i>et al</i> ^[19]	2007	Prospective, multi-center (post-hoc)	800	580	40	3	0	57	61	39	0
DeEugenio, <i>et al</i> ^[20]	2007	Retrospective, 1-center	194	97	60	10	1	29	-	-	-
Karjalainen, <i>et al</i> ^[21]	2007	Retrospective, multi-center	478	106	70	4	11	15	9	46	45
Manzano-Fernandez, <i>et al</i> ^[22]	2008	Retrospective, 1-center	104	51	100	-	-	-	37	54	9
Rogacka, <i>et al</i> ^[23]	2008	Retrospective, 1-center	127	127	59	12	0	19	3	23	74
Rossini, <i>et al</i> ^[24]	2008	Prospective, multi-center	204	102	67	0	0	33	34	44	22
Sarafoff, <i>et al</i> ^[25]	2008	Prospective, 1-center	515	306	67	17	0	16	-	-	-
Maegdefessel, <i>et al</i> ^[26]	2008	Retrospective, 1-center	159	14	100	-	-	-	32	54	14
Haelg, <i>et al</i> ^[27]	2009	Prospective, multi-center (post-hoc)	813	44	-	-	-	-	16	41	43
Halbfass, <i>et al</i> ^[28]	2009	Retrospective, 1-center	117	53	100	-	-	-	-	-	-
Helft G, <i>et al</i> ^[29]	2009	Prospective, 1-center	50	50	62	24	0	14	-	-	72
Rubboli, <i>et al</i> ^[30]	2009	Prospective, multi-center	163	111	84	9	2	5	21	51	28
Olson, <i>et al</i> ^[31]	2009	Retrospective, 1-center	514	175	24	1	1	74	-	-	-
Sambola, <i>et al</i> ^[32]	2009	Prospective, multi-center	405	278	65	17	1	17	-	-	-
Gilard, <i>et al</i> ^[33]	2009	Prospective, multi-center	359	125	63	18	0	19	8	39	53
Baber, <i>et al</i> ^[34]	2009	Retrospective, 1-center	454	170	45	6	8	41	-	-	85
Gao, <i>et al</i> ^[35]	2010	Prospective, 1-center	622	142	100	-	-	-	12	-	-
Uchida, <i>et al</i> ^[36]	2010	Retrospective, 1-center	575	50	58	6	10	26	12	18	60
Ziakas, <i>et al</i> ^[37]	2010	Prospective, 1-center	56	56	66	9	13	12	-	-	52
Persson, <i>et al</i> ^[38]	2010	Prospective, multi-center (post-hoc)	27,972	659	-	-	-	-	10	80	10

VKA: vitamin K-antagonists; PCI-S: percutaneous coronary intervention with stent implantation. TT: triple therapy; AF: atrial fibrillation; STEMI: ST-elevation myocardial infarction; NSTE-ACS: non ST-elevation acute coronary syndromes; PTS: patients.

Table 2. Procedural characteristics in the various studies.

Ref.	Year	Radial approach (%)	GP IIb/IIIa (%)	Bridging heparin (%)
Orford, <i>et al</i> ^[12]	2004	14	48.0	-
Mattichak, <i>et al</i> ^[13]	2005	-	2.5	-
Khurram, <i>et al</i> ^[14]	2006	-	-	-
Konstantino, <i>et al</i> ^[15]	2006	-	38.2	-
Lip & Karpha ^[16]	2006	-	-	-
Porter, <i>et al</i> ^[17]	2006	-	47.7	69.0
Rubboli, <i>et al</i> ^[18]	2007	0	20.0	25.0
Nguyen, <i>et al</i> ^[19]	2007	-	61.0	-
DeEugenio, <i>et al</i> ^[20]	2007	-	43.0	-
Karjalainen, <i>et al</i> ^[21]	2007	21	28.0	-
Manzano-Fernandez, <i>et al</i> ^[22]	2008	28	39.0	-
Rogacka, <i>et al</i> ^[23]	2008	-	-	-
Rossini, <i>et al</i> ^[24]	2008	32	47.0	-
Sarafoff, <i>et al</i> ^[25]	2008	-	-	100.0
Maegdefessel, <i>et al</i> ^[26]	2008	-	-	-
Haelg, <i>et al</i> ^[27]	2009	0	27.0	-
Halbfass, <i>et al</i> ^[28]	2009	-	-	-
Helft, <i>et al</i> ^[29]	2009	100	12.0	0.0
Rubboli, <i>et al</i> ^[30]	2009	39	11.0	-
Olson, <i>et al</i> ^[31]	2009	-	-	-
Sambola, <i>et al</i> ^[32]	2009	23	9.7	-
Gilard, <i>et al</i> ^[33]	2009	66	6.0	0.0
Baber, <i>et al</i> ^[34]	2009	-	38.0	-
Gao, <i>et al</i> ^[35]	2010	40	12.2	88.0
Uchida, <i>et al</i> ^[36]	2010	-	-	-
Ziakas, <i>et al</i> ^[37]	2010	48	-	-
Persson, <i>et al</i> ^[38]	2010	-	-	-

GP IIB/IIIA: glycoprotein IIb/IIIa inhibitors.

The incidence of major and minor bleedings reported at the various time points of follow-up is reported in Table 4.

4 Discussion

As derived from the above data, definitive conclusions regarding the true safety of TT appear currently precluded. Apart from acknowledging that the overall population on TT which has been examined so far accounts for only about 4,000 patients, it must be noted that the analyses of the data were carried out retrospectively in 70% of the studies. While being subject to biases of various nature, the analyses did not correlate the bleeding event with the antithrombotic treatment actually ongoing at the time of complication. It is obvious that hemorrhagic complications occurring weeks or months after TT has been completed, cannot plausibly be attributed to this regimen, even though the analysis is carried out according to the initially assigned treatment. Indeed, in one study where such evaluation was carried out,^[27] in half of patients who had been initially treated with TT clopidogrel had already been withdrawn at the time of bleeding, when only the combination of VKA and aspirin was ongoing.

The international normalized ratio (INR) value at the time of bleeding was reported in 5 studies (19%) for major

Table 3. Incidence of major and minor bleeding at follow-up in the various studies.

Ref.	Year	Major bleeding (%)					Minor bleeding (%)				
		In Hospital	≤ 1 mo	6 mo	12 mo	> 12 mo	In Hospital	≤ 1 mo	6 mo	12 mo	> 12 mo
Orford, <i>et al</i> ^[12]	2004	-	3.1	-	-	-	-	6.1	-	-	-
Mattichak, <i>et al</i> ^[13]	2005	-	-	12.5	21.0	-	-	-	-	-	-
Khurram, <i>et al</i> ^[14]	2006	-	-	6.6	-	-	-	-	14.9	-	-
Konstantino, <i>et al</i> ^[15]	2006	2.6	-	-	-	-	-	-	-	-	-
Lip & Karpha ^[16]	2006	-	-	-	17.0	-	-	-	-	-	-
Porter, <i>et al</i> ^[17]	2006	-	1.1	-	-	-	-	10.0	-	-	-
Rubboli, <i>et al</i> ^[18]	2007	-	15.0	-	-	-	-	5.0	-	-	-
Nguyen, <i>et al</i> ^[19]	2007	5.9	-	-	-	-	-	-	-	-	-
DeEugenio, <i>et al</i> ^[20]	2007	-	-	14.4	-	-	-	-	-	-	-
Karjalainen, <i>et al</i> ^[21]	2007	-	-	-	6.6	-	-	-	-	-	-
Manzano-Fernandez, <i>et al</i> ^[22]	2008	5.8	-	-	21.6	-	-	-	-	-	-
Rogacka, <i>et al</i> ^[23]	2008	-	-	-	-	4.7	-	-	-	-	2.4
Rossini, <i>et al</i> ^[24]	2008	-	1.0	-	-	2.9	-	2.9	-	-	7.8
Sarafoff, <i>et al</i> ^[25]	2008	-	-	-	1.3	1.4	-	-	-	7.2	7.7
Maegdefessel, <i>et al</i> ^[26]	2008	-	-	-	0.0	-	-	-	-	0.0	-
Haelg, <i>et al</i> ^[27]	2009	-	-	-	6.1	-	-	-	-	-	-
Halbfass, <i>et al</i> ^[28]	2009	-	-	-	-	2.0	-	-	-	-	-
Helft, <i>et al</i> ^[29]	2009	-	-	-	-	-	-	2.0	-	-	-
Rubboli, <i>et al</i> ^[30]	2009	2.0	-	-	-	-	-	-	-	-	-
Olson, <i>et al</i> ^[31]	2009	-	-	-	14.3	-	-	-	-	-	-
Sambola, <i>et al</i> ^[32]	2009	-	-	3.4	-	-	-	-	11.2	-	-
Gilard, <i>et al</i> ^[33]	2009	1.6	-	3.2	5.6	-	-	-	-	-	-
Baber, <i>et al</i> ^[34]	2009	1.1	-	-	-	-	-	-	-	-	-
Gao, <i>et al</i> ^[35]	2010	-	-	-	2.9	-	-	-	-	-	-
Uchida, <i>et al</i> ^[36]	2010	-	-	-	-	20.0	-	-	-	-	20.0
Ziakas, <i>et al</i> ^[37]	2010	4.0	-	-	-	-	-	-	-	-	-
Persson, <i>et al</i> ^[38]	2010	-	-	-	3.0	-	-	-	-	-	-

Table 4. Incidence of major/minor bleeding at various time points of follow-up, data are presented as mean \pm SD.

	Major bleeding (%)	Minor bleeding (%)
In-hospital	3.3 \pm 1.9	NR
\leq 1 mo	5.1 \pm 6.7	5.2 \pm 3.1
6 mo	8.0 \pm 5.2	13.1 \pm 2.6
12 mo	9.0 \pm 8.0	3.6 \pm 5.1
\geq 12 mo	6.2 \pm 7.8	9.5 \pm 7.5

NR: not reported.

bleeding and in 3 (11%) for minor bleedings. As regards major bleedings, the INR value was above the therapeutic range in 35% of patients (range 0%–100%).

Also, no valuable information about the INR value at the time of bleeding, which has been shown to increase the risk of bleeding in patients on TT when above a cut-off value of 2.6,^[24] can be obtained from the available studies. While in one study all patients experiencing a major bleeding had the INR above the therapeutic range, in two studies major bleeding occurred regardless of the fact that the INR was within the therapeutic range (Table 3).

When focusing on the absolute incidence of major bleeding, an increase is apparent as follow-up prolongs (Table 4). While acknowledging that a more prolonged exposure to TT may intuitively be associated with and increased risk of bleeding, it should be noted once again that clear information about the ongoing treatment throughout the entire duration of follow-up is lacking. It is of note, however, that the in-hospital major bleeding rate was limited to about 3% (Table 3). Such figure is not substantially different from that reported in the overall population of patients undergoing PCI-S,^[39] therefore supporting the concept that TT in itself does not substantially impact on the incidence of early major bleeding. Further reduction of the in-hospital major bleeding rate may probably be obtained by more extensively using the radial approach, which has been shown to virtually eliminate the occurrence of bleeding at the vascular access site,^[40] and by further limiting the use of glycoprotein IIb/IIIa inhibitors, as well as of heparin bridging strategies following the (likely unnecessary) peri-procedural withdrawal of VKA, which both have been found associated with early hemorrhagic complications.^[41,42]

When examining the absolute incidence of major bleeding after discharge, it should be noted that the figures are not substantially different from those reported with DAPT, for example in the CREDO trial.^[43] In this study, the 1- and 12-month incidence of major bleeding was 4.7% and 8.8%, respectively, as compared to the average 5.1% and 9.0%, respectively, reported in patients receiving

TT (Table 3). Subtracting the about 3% rate of in-hospital bleeding, which as previously mentioned has more to do with procedural variables than with TT itself, the true incidence of major bleeding during medium-term follow-up should be more likely in the reassuring order of 2% to 6%. Indeed, these figures have been reported in better quality studies, such those prospective and with a tight control of the INR which was also targeted to the lower end of the therapeutic range.^[7,24,25,32,33]

The lower incidence of major bleeding at a follow-up longer than 12 months may be explained by the limited number of studies reporting on that and by the variable duration of follow-up following the first year. Also not surprisingly is the non-linear course, as well as the variable absolute incidence, of minor bleedings because they often go undetected not inducing patients to seek medical attention.

4.1 Conclusions

TT with VKA, aspirin and clopidogrel is the recommended antithrombotic regimen following PCI-S in patients with an indication for VKA. Although being not clear-cut, current available evidence suggests that TT is associated with an increased risk of bleeding, apparently increasing as treatment prolongs. The absolute incidence of major bleeding at short- to medium-term follow-up appears not substantially different from that of DAPT, which however cannot be used alone in these patients because of the high risk of thromboembolic and thrombotic complications. Since major bleedings may be life threatening or may determine the withdrawal of one or more of the antithrombotic agents (therefore exposing patients to the risks of thromboembolism and/or stent thrombosis),^[44] and minor bleedings may induce physicians or patients to withdraw clopidogrel (again exposing patients to the potentially catastrophic stent thrombosis),^[45] it is prudent to limit the duration of TT for as short as possible, therefore using drug-eluting stents restrictively. However, when drug-eluting stent implantation is clinically necessary, the use of newer generation drug-eluting stents (especially polymer-free) that exhibit accelerated reendothelialization is preferred.^[10] This does not imply that patients receiving a newer generation drug-eluting stent should receive clopidogrel for $<$ 12 months (current guidelines recommend at least 12 months of clopidogrel therapy following drug-eluting stent implantation),^[46] but rather the use of newer generation drug-eluting stent allows for the safer early interruption of clopidogrel if the need should arise.^[10] Finally, throughout TT, which should be limited to three to six months in VKA patients

undergoing PCI-S in the context of an acute coronary syndrome (where current guidelines recommend 12 months of clopidogrel treatment),^[47] the INR should be frequently and carefully monitored, along with being targeted at the lower end of the therapeutic range (*i.e.*, 2.0 to 2.5 in patients with atrial fibrillation).^[2,3]

While waiting for the ongoing, large-scale, registries and clinical trials to clarify the few facts and to answer the many questions regarding the risk of bleeding of TT, this treatment should not be denied to patients with an indication for VKA undergoing PCI-S provided that the above mentioned measures and cautions are implemented.

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