REVIEW

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Combining Antiplatelet and Antithrombotic Therapy (Triple Therapy): What Are the Risks and Benefits?

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ABSTRACT

Most patients with mechanical heart valves and many patients with atrial fibrillation will require long-term anticoagulation therapy. For patients with mechanical prosthetic valves, only warfarin is indicated. However, for patients with nonvalvular atrial fibrillation who are at increased risk for embolic stroke, one of the newer antithrombotic medications, such as rivaroxaban, dabigatran, and apixaban, also can be used. Patients with indications for antithrombotic therapy often will have coexisting vascular disease, such as coronary artery disease, requiring concomitant antiplatelet therapy with aspirin alone or more commonly with a dual antiplatelet regimen, aspirin and clopidogrel, or prasugrel or ticagrelor. The risks and benefits of this approach are still not well defined, and current guidelines have included recommendations based primarily on expert opinion.

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KEYWORDS: Acute coronary syndrome; Anticoagulation; Antithrombotic therapy; Aspirin; Atrial fibrillation; Clopidogrel; Coronary intervention; Coronary stent; Drug-eluting stent; Platelet inhibitor; Stent; Triple therapy; Warfarin

The use of long-term oral anticoagulation is indicated in a number of different clinical situations, including atrial fibrillation with increased risk for arterial embolism and in patients with mechanical heart valves.[1] Atrial fibrillation affects more than 1% of the US population and substantially increases the risk for stroke. It is known that oral anticoagulation therapy reduces stroke incidence by two thirds compared with placebo treatment; compared with aspirin, oral anticoagulation therapy reduces the risk of stroke by 45%. The number of patients who need to be treated for 1 year with oral anticoagulation therapy to prevent 1 stroke is approximately 100. At the same time, oral anticoagulation increases the risk of major bleeding by approximately 70% compared with aspirin.[2]

Atrial fibrillation with concomitant coronary artery disease requiring percutaneous coronary intervention is present in 20% to 30% of patients with atrial fibrillation,[1] thus requiring a dual antiplatelet regimen with aspirin and clopidogrel or other adenosine diphosphate inhibitor to prevent stent thrombosis. In addition, antithrombotic therapy will be indicated in a substantial number of these individuals. The recommended length of treatment with dual antiplatelet therapy is variable, ranging from 4 weeks after bare-metal stent implantation to at least 6 to 12 months with drug-eluting stents.[3] In patients with acute coronary syndromes, clopidogrel is indicated for up to 12 months after coronary intervention. Approximately 10% of patients who undergo percutaneous coronary intervention also will have a clear indication for long-term anticoagulation therapy, for example, atrial fibrillation with increased stroke risk.[4]

The use of warfarin plus both aspirin and clopidogrel has been referred to as "triple therapy," and it represents a medical decision-making challenge, because it decreases the risk of thrombotic events together with an increased risk for bleeding complications.[3] This is especially challenging among elderly patients, in whom the risks of stroke and bleeding are higher and physicians tend to "undermedicate" because of the fear of complications, as observed in large patient databases in which less than 40% of patients aged $\geq$80 years with both coronary artery disease and atrial fibrillation with a $CHADS_2$ score $\geq$2 are prescribed warfarin for thromboembolic prophylaxis.[5]

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Antiplatelet therapy is used for secondary prevention of ischemic events in patients with established coronary artery disease.[6] The Antithrombotic Trialist Collaboration Group meta-analysis showed that antiplatelet therapy reduces the occurrence of nonfatal myocardial infarction, stroke, or vascular events.[7] Rupture or erosion of an atherosclerotic plaque that results in partial or complete occlusion of a coronary artery is the most common mechanism responsible for acute coronary syndrome. Plaque rupture exposes the subendothelial matrix, rich in tissue factor, to the circulating blood with resultant activation and aggregation of platelets and subsequent thrombus formation. Two types of thrombi can form after plaque rupture or erosion: a platelet-rich clot, seen in patients with unstable angina/non-ST-elevation myocardial infarction, and a fibrin-rich clot, seen in patients with ST-elevation myocardial infarction.[8-10] In patients with ST-elevation myocardial infarction, management focuses on restoration of blood flow in the infarcted artery.[11] In contrast, in unstable angina/non-ST-elevation myocardial infarction, the goal of antiplatelet therapy is to prevent further thrombosis and to allow endogenous fibrinolysis to dissolve the existing thrombus and thereby reduce the degree of coronary obstruction.[12,13]

Dual antiplatelet therapy with aspirin and clopidogrel after coronary intervention is superior to therapy with the combination of aspirin and oral anticoagulant.[14] Current guidelines (see next section) recommend that all patients with unstable angina/non-ST-elevation myocardial infarction should receive aspirin indefinitely (level of evidence A) and dual aspirin/clopidogrel antiplatelet therapy up to 12 months (level of evidence B) even in non-stented patients.[15]

CLINICAL SIGNIFICANCE

- The combination of chronic oral anticoagulation and antiplatelet therapy is a common therapeutic regimen encountered in the daily practice of physicians.
- It is uncertain which regimen provides the most benefit with the least rate of complications.
- We seek to describe the most appropriate therapeutic schema with a review of the most recent data available.

WHAT DO CURRENT GUIDELINES RECOMMEND?

The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines on atrial fibrillation management were recently published, and they acknowledge that no adequate studies specifically address the issue of dual antiplatelet therapy in patients who also require chronic anticoagulation because of atrial fibrillation, and recommendations are based primarily on consensus. These guidelines suggest that in patients with long-standing atrial fibrillation and moderate to high risk of thromboembolism on the basis of a Cardiac failure or dysfunction, Hypertension, Age $\geq$75 [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65-74, and Sex category [female] (CHA_2DS_2-VASc) score $>$2, the maintenance regimen should be a combination of aspirin, clopidogrel, and warfarin; efforts should be directed to minimize the duration of triple therapy; and the choice of a stent should include consideration of the potential requirement for long-term anticoagulant therapy.[16] Use of dual antiplatelet therapy alone may be considered for patients with acute coronary syndrome who have atrial fibrillation and a low $CHADS_2$ score. Other authorities have suggested an antithrombotic management scheme based on the acute coronary syndrome presentation, perceived bleeding risk, and type of stent used.[3]

HOW SAFE IS IT TO USE TRIPLE THERAPY?

The risk of bleeding increases in patients receiving chronic anticoagulant therapy when an antiplatelet agent is added, for example, in patients with coronary artery disease after a coronary intervention. These are the patients in whom a medical dilemma exists, as one tries to balance the risk of thrombotic events versus the risk of bleeding complications. Unfortunately, the combination of oral anticoagulants and antiplatelet therapy is associated with a high annual risk (4%-16%) of fatal and nonfatal bleeding episodes.[1]

A retrospective trial involving 426 patients concluded that in patients with atrial fibrillation treated with percutaneous coronary intervention with or without stents who have a low risk of bleeding complications, triple-therapy regimen should be the antithrombotic drug treatment approach.[3] Orford et al[17] showed an overall bleeding rate of 9.2% with the use of triple therapy in a small group of patients. Khurram et al[18] found that in patients requiring anticoagulation therapy with warfarin, the addition of dual antiplatelet therapy was associated with a 6.6% major bleeding risk. Rogacka et al[19] found a 4.7% incidence of major bleeding complications during the triple therapy. Bleeding commonly occurred within the first month of triple therapy in the majority of patients.[19]

IS THERE BENEFIT IN USING DOUBLE THERAPY WITH REGARD TO BLEEDING RISK?

As already noted, patients receiving triple therapy are at increased risk for minor and major bleeding complications. Until recently, there has not been a controlled trial addressing this issue, with most of the recommendations and guidelines being based on retrospective studies and expert recommendations. Last year, the results of the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) study were published. This was a multicenter randomized controlled trial that included patients receiving chronic anticoagulation therapy undergoing coronary artery intervention. Patients were randomized into 2 groups: warfarin plus clopidogrel and aspirin versus warfarin plus clopidogrel alone.

The primary end point was the number of all-cause bleeding events. This trial demonstrated a significant decrease in bleeding complications in the double therapy group compared with patients receiving triple therapy. Although there was a difference in the number of minor versus major bleeding events, depending on the bleeding criteria used, the overall bleeding occurrence of both mild and severe bleeding was higher in the triple therapy group (**Table 1**). These findings suggest that the antithrombotic regimen in patients requiring chronic anticoagulation and coronary artery disease after coronary intervention requiring antiplatelet therapy with the least bleeding complications should include the combination of warfarin and clopidogrel.

The decision regarding the choice among the different antithrombotic regimens also will depend on the risk of thromboembolic events, where low-risk patients with an indication for oral anticoagulation therapy may obtain the same benefit with a dual antiplatelet regimen compared with triple therapy with a lower risk of bleeding. This was observed in a prospective multicenter registry in 2009 that included 405 individuals. Patients at low thromboembolic risk assigned to dual antiplatelet therapy showed the lowest rate of bleeding events and a similar efficacy to triple therapy in preventing major adverse cardiovascular events.[20] This suggests that the use of triple therapy should be reserved for patients at moderate to high risk of thromboembolic events.

A recent retrospective cohort study of veterans comparing patients with different complex antithrombotic regimens for the incidence of gastrointestinal bleeding events, identifying the number needed to harm, demonstrated that as few as 52 patients (95% confidence interval [CI], 20-210) prescribed triple therapy, 56 patients prescribed a combination of aspirin plus warfarin (95% CI, 22-231), and 65 patients prescribed a combination of warfarin plus clopidogrel (95% CI, 24-379) would result in 1 additional upper gastrointestinal bleeding event. There also was an increased risk of requiring a blood transfusion with the combination of warfarin plus aspirin (hazard ratio [HR], 6.1; 95% CI, 5.2-7.1) and triple therapy (HR, 5.0; 95% CI, 4.2-5.8), with a lower risk with the combination of warfarin plus clopidogrel (HR, 3.5; 95% CI, 3.0-4.2). The incidence of lower gastrointestinal bleeding events was 30% higher with the combination of warfarin plus clopidogrel.[21]

DOES DOUBLE THERAPY COMPARED WITH TRIPLE THERAPY INCREASE THE RISK OF THROMBOTIC COMPLICATIONS?

The combination of warfarin and aspirin after coronary intervention has been shown to be less effective in preventing stent thrombosis compared with clopidogrel plus aspirin, as observed by Ruiz-Nodar et al[3] in a series of patients with atrial fibrillation undergoing coronary intervention, in whom omission of anticoagulation therapy at the time of discharge was associated with a higher incidence of mortality and major adverse cardiovascular events.

The same findings were then demonstrated in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events-Warfarin (ACTIVE-W) trial in patients with atrial fibrillation treated with dual antiplatelet therapy compared with warfarin alone. Patients were eligible for this trial if they had electrocardiographic evidence of atrial fibrillation and at least one of the following: age more than 75 years, systemic hypertension on medical therapy, prior

Table 1 Results for the Primary End Point at 1 Year (WOEST Study)

	Double Therapy (n = 279)	Triple Therapy (n = 284)	Hazard Ratio (95% CI)	*P* Value
Any bleeding event	54 (19.4%)	126 (44.4%)	0.36 (0.26-0.50)	<.0001
TIMI bleeding				
Major	9 (3.2%)	16 (5.6%)	0.56 (0.25-1.27)	.159
Minor	39 (14.0%)	89 (31.3%)	0.40 (0.27-0.58)	<.0001
GUSTO bleeding				
Severe	4 (1.4%)	10 (3.5%)	0.40 (0.12-1.27)	.119
Severe and moderate	15 (5.4%)	35 (12.3%)	0.42 (0.23-0.76)	.003
BARC bleeding				
3	18 (6.5%)	36 (12.7%)	0.49 (0.28-0.86)	.011
3c	3 (1.1%)	3 (1.1%)	1.00 (0.20-4.90)	.996
3b	6 (2.2%)	14 (5.0%)	0.43 (0.17-1.10)	.074
3a	9 (3.2%)	19 (6.7%)	0.47 (0.21-1.00)	.054
2	23 (8.2%)	59 (20.8%)	0.36 (0.23-0.59)	<.0001
2+3	40 (14.3%)	90 (31.7%)	0.40 (0.28-0.58)	<.0001
1	18 (6.5%)	45 (15.8%)	0.38 (0.22-0.66)	.0004
Any blood transfusion	11 (3.9%)	27 (9.5%)	0.39* (0.17-0.84)	.011

BARC = Bleeding Academic Research Consortium criteria; CI = confidence interval; GUSTO = Global Utilization Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria; TIMI = thrombolysis in myocardial infarction criteria; WOEST = What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.

*Odds ratio.

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stroke or transient ischemic attack, prior systemic embolism, systolic dysfunction with left ventricular ejection fraction less than 45%, peripheral arterial disease, diabetes mellitus, or prior coronary artery disease. More than 6500 patients were randomized to aspirin plus clopidogrel or a vitamin K antagonist alone. The end point in this trial was the number of cardioembolic strokes. The ACTIVE-W trial was halted early by the data monitoring committee because of the clear superiority of oral anticoagulation over dual antiplatelet therapy with aspirin plus clopidogrel (**Figure 1**).

The combination of aspirin and warfarin seems to be the worst therapeutic combination in terms of stent thrombosis, thromboembolism, and bleeding occurrence, and for this reason should not be prescribed as the initial management in the immediate period after coronary intervention or stent placement.[22] Similar results were reported by Karjalainen et al,[4] who compared different antithrombotic regimens for the occurrence of major adverse cardiovascular events. There was a higher incidence of stent thrombosis in patients receiving warfarin plus aspirin compared with patients receiving triple therapy (15.2% vs 1.9%, $P = .004$)[4] (**Figure 2**).

The combination of clopidogrel and warfarin seems to be the most reasonable choice for the patient group just discussed in an attempt to reduce bleeding events without significantly increasing the incidence of thrombotic complications. This has been suggested by previous retrospective and a few smaller prospective trials. In 2010, Gao et al[23] compared different antithrombotic strategies in a prospective study in more than 600 patients and confirmed the benefit of triple therapy in decreasing the rate of major adverse cardiovascular events. However, these authors also noted a comparably low incidence of stroke in patients taking a combination of warfarin and either dual or single antiplatelet therapy (0.7% vs 0.8%), as well as a similar rate of major adverse cardiovascular events in both groups, which was thought to be, in part, explained by the high proportion of clopidogrel use (109/125, 87.2%) in the group assigned to warfarin plus a single antiplatelet agent. These results suggested that the combination of warfarin and a single antiplatelet therapy (ie, clopidogrel) was an acceptable treatment option in patients whose bleeding risk outweighed the risk of stroke.[23] Further confirmation of this concept was recently demonstrated in the WOEST trial that showed no difference in the rate of thrombotic complications in patients assigned to the group taking warfarin and clopidogrel compared with those individuals taking triple therapy. Although the study was not powered for this end point, it is unlikely that a major clinical trial will be conducted in the future to answer this specific question (**Table 2**).

DOES ANY EVIDENCE EXIST CONCERNING THE USE OF THE NEWER ANTICOAGULANTS IN COMBINATION WITH PLATELET ANTAGONISTS?

Several new antithrombotic agents recently have been approved by the Food and Drug Administration for a number of indications, including nonvalvular atrial fibrillation. The new agents are dabigatran, rivaroxaban, and most recently apixaban. There also are a number of new platelet inhibitors available for clinical use. These agents are similar to clopidogrel (ie, prasugrel and ticagrelor) and have specific indications. Currently, it is not unusual to have patients on different regimens of "modified" double or triple therapy involving 1 or more of these new agents. Clearly, therapy with the new agents represents an even bigger clinical challenge for medical decision-making involving an attempt to balance the risk of bleeding versus the risk of thrombotic complications. Unfortunately, at this time there are even less

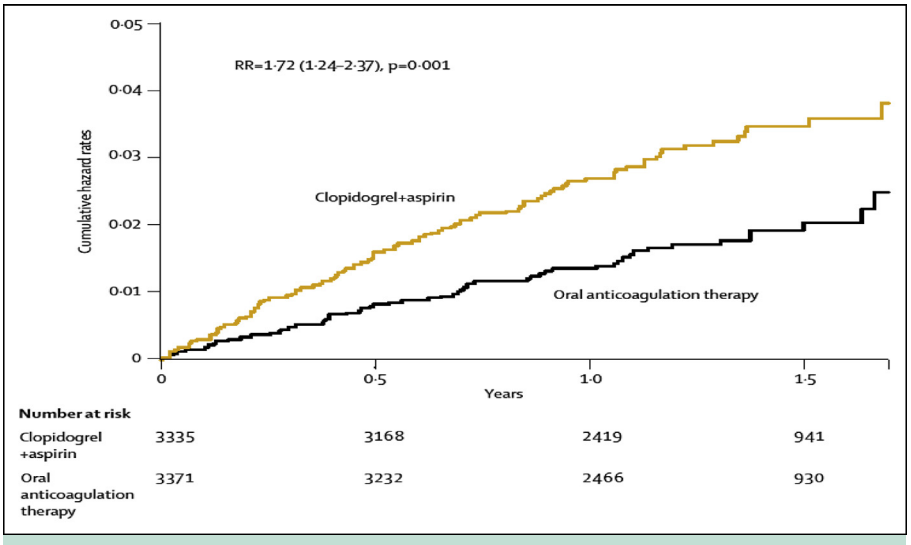

Figure 1 Cumulative risks for stroke with the 2 treatments (figure from the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events, reproduced with permission). RR = relative risk.

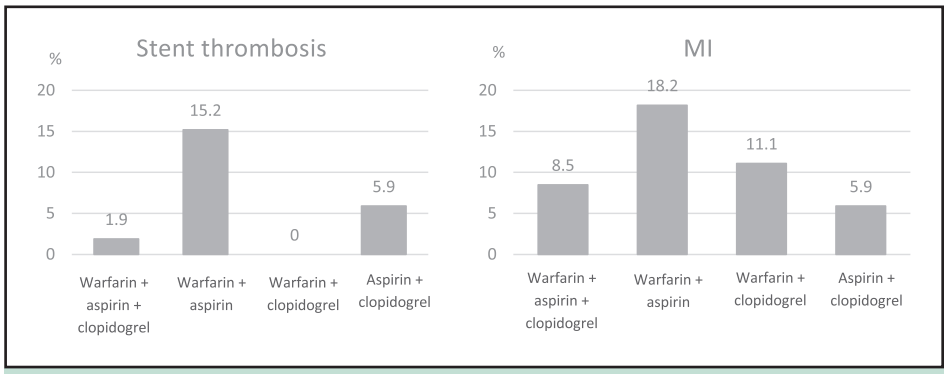

Figure 2 Complications during 12-month follow-up with various drug regimens adopted after stenting in warfarin group. Reproduced and modified with permission from the study by Karjalainen et al.[4] MI = myocardial infarction.

data to support the clinical use of various combinations of these new agents. To date, there are no guideline recommendations addressing this problem because of lack of evidence. Patients taking these newer medications were not included in the WOEST trial, and it is not possible to extrapolate the results of this study to clinical scenarios involving the newer antithrombotic medications. In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was an open-label randomized comparison of dabigatran and warfarin in patients with atrial fibrillation that showed noninferiority of dabigatran in the primary outcome of stroke and systemic embolism, it was observed that concomitant aspirin use in patients taking dabigatran was an independent risk factor for intracranial hemorrhage, suggesting that it should be avoided during dabigatran therapy when possible.

Table 2 Secondary and Safety End Points at 1 Year (WOEST Study Table)

	Double Therapy (n = 279)	Triple Therapy (n = 284)	Hazard Ratio (95% CI)	*P* Value
Combined secondary end point	31 (11.1%)	50 (17.6%)	0.60 (0.38-0.94)	.025
Death				
All-cause	7 (2.5%)	18 (6.3%)	0.39 (0.16-0.93)	.027
Cardiac	3 (1.1%)	7 (2.5%)	0.43 (0.11-1.66)	.207
Noncardiac	4 (1.4%)	11 (3.9%)	0.36 (0.11-1.13)	.069
Myocardial infarction				
Any	9 (3.2%)	13 (4.6%)	0.69 (0.29-1.60)	.382
STEMI	1 (.4%)	3 (1.1%)	0.34 (0.04-3.25)	.325
Non-STEMI	8 (2.9%)	10 (3.5%)	0.79 (0.31-2.01)	.625
Target-vessel revascularization				
PCI or CABG	20 (7.2%)	19 (6.7%)	1.05 (0.56-1.97)	.876
PCI	17 (6.1%)	16 (5.6%)	1.06 (0.54-2.10)	.869
CABG	3 (1.1%)	3 (1.1%)	1.00 (0.20-4.90)	.998
Stroke				
Any	3 (1.1%)	8 (2.8%)	0.37 (0.10-1.40)	.128
Ischemic	2 (0.7%)	8 (2.8%)	0.25 (0.05-1.17)	.056
Hemorrhagic	1 (0.4%)	0	NA	.321
Disabling	2 (0.7%)	2 (0.7%)	0.99 (0.14-6.99)	.988
Nondisabling	1 (0.4%)	7 (2.5%)	0.14 (0.02-1.16)	.034
Stent thrombosis				
Any	4 (1.4%)	9 (3.2%)	0.44 (0.14-1.44)	.165
Definite	1 (0.4%)	3 (1.1%)	0.33 (0.03-3.22)	.319
Probable	0	2 (0.7%)	NA	.161
Possible	3 (1.1%)	4 (1.4%)	0.75 (0.17-3.30)	.708

CABG = coronary artery bypass graft; NA = not applicable; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction; WOEST = What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.

Reproduced and modified with permission from the WOEST study.

DISCUSSION

The American and European guidelines recommend the institution of triple therapy with aspirin, clopidogrel, and oral anticoagulant agents for those patients taking long-term anticoagulation for atrial fibrillation or with mechanical valves who undergo percutaneous coronary intervention.[16] In the absence of guidance from randomized clinical trials and large-scale registries, physicians have adopted different approaches to treatment with antithrombotic therapies, especially in patients who present with acute coronary syndrome and in whom a concomitant indication for warfarin is present. This was observed in the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines registry, which showed that approximately one third of patients with acute coronary syndrome who were taking warfarin at the time of admission to the hospital had discontinuation of warfarin when dual antiplatelet therapy was started after coronary intervention.[24]

The existing evidence to date suggests that in those patients with an indication for triple therapy, it is safe to stop aspirin, thereby decreasing the risk of bleeding events without significantly increasing the risk of thrombotic complications. Careful attention to the monitoring of the international normalized ratio results and strict adherence to recommended levels of systemic anticoagulation are important in these patients to decrease the incidence of bleeding.[4] Some experts advocate the use of lower levels of warfarin anticoagulant control when dual antiplatelet therapy is added. However, it is unknown at this time whether this alteration in warfarin therapy will be effective in reducing bleeding complications without increasing the risk of thrombotic events. Frequent and close monitoring of the international normalized ratio, which should be preferably targeted at the lower end of the therapeutic range, should be maintained during the duration of combined antithrombotic and antiplatelet therapy.[6] Risk stratification for bleeding before coronary intervention is strongly encouraged, with particular attention paid to stent type selection, which will influence the length of antiplatelet therapy. The choice of antithrombotic therapy for patients with coronary artery disease and atrial fibrillation requires careful evaluation of safety and efficacy, particularly in elderly patients at greater risk for bleeding and thromboembolic events.[5]

It has been demonstrated that oral anticoagulation therapy is superior to clopidogrel plus aspirin for the prevention of thrombotic vascular events in patients with atrial fibrillation who are at increased risk for stroke. This was demonstrated in the ACTIVE-W study, which had to be stopped early because of clear superiority of oral anticoagulation. Another important finding was that patients with therapeutic international normalized ratio levels were the individuals who showed actual benefit from anticoagulation therapy.[2] On the other hand, multiple randomized clinical trials have shown that the combination of aspirin plus warfarin after coronary intervention is not as effective as dual antiplatelet therapy with an adenosine diphosphate receptor antagonist in addition to aspirin for preventing stent thrombosis.[16]

CONCLUSIONS

Newer evidence provided by the WOEST study shows that patients taking oral anticoagulation who undergo percutaneous coronary intervention and are treated with clopidogrel alone plus warfarin have a significantly lower risk of bleeding complications compared with patients receiving triple therapy, that is, the combination of aspirin, clopidogrel, and warfarin. It seems that the risk of thrombotic complications with warfarin plus clopidogrel is not increased.[1] However, the number of patients treated in the WOEST trial was small and not powered to answer this question concerning dual versus triple anticoagulant therapy. Nevertheless, it is unlikely that a large randomized controlled trial will be conducted for the purpose of answering this question in the future. For this reason, the antithrombotic regimen selected by the physician in these patients should be individualized for each patient depending on the perceived risk of thromboembolism and stent thrombosis, as well as the risk for bleeding complications.[3]

Whether current recommendations can be applied to modified double or triple therapy regimens by combining newer antiplatelet agents (ie, prasugrel or ticagrelor) and newer anticoagulants (ie, ribaroxaban, dabigatran or apixaban) remains to be studied.

References

1. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trial. *Lancet*. 2013;381:1107-1115.
2. Connolly S, Yusuf S, Camm J, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomized controlled trial. *Lancet*. 2006;367:1903-1912.
3. Ruiz-Nodar JM, Marin F, Furtado JA, et al. Anticoagulant and antiplatelet therapy use in 426 patients with atrial fibrillation undergoing percutaneous coronary intervention and stent implantation implications for bleeding risk and prognosis. *J Am Coll Cardiol*. 2008;51:818-825.
4. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. *Eur Heart J*. 2007;28:726-732.
5. Hess CN, Broderick S, Piccini JP, et al. Antithrombotic therapy for atrial fibrillation and coronary artery disease in older patients. *Am Heart J*. 2012;164:607-615.
6. Becker RC, Meade TW, Berger PB, et al. The primary and secondary prevention of coronary artery disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(6 Suppl):776s-814s.
7. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002;324:71-86.
8. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. *Circulation*. 2003;108:1664-1672.
9. Mizuno K, Satomura K, Miyamoto A, et al. Angioscopic evaluation of coronary-artery thrombi in acute coronary syndromes. *N Engl J Med*. 1992;326:287-291.

10. Sullivan E, Kearney M, Isner JM, Topol EJ, Losorda DW. Pathology of unstable angina: analysis of biopsies obtained by directional coronary atherectomy. *J Thromb Thrombolysis*. 1994;1:63-71.
11. Cannon CP, Braunwald E. Time to reperfusion: the critical modulator in thrombolysis and primary angioplasty. *J Thromb Thrombolysis*. 1996;3:117-125.
12. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1983;309:396-403.
13. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
14. Rubboli A, Milandri M, Castelvetri C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting. Clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. *Cardiology*. 2005;104:101-106.
15. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2012;60:645-681.
16. January CT, Wann LS, Alpert JS, et al. 2014 ACCF/AHA/HRS Guideline for the management of patients with atrial fibrillation. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the Heart Rhythm Society. *J Am Coll Cardiol*. 2004. [Epub ahead of print].
17. Orford JL, Fasseas P, Melby S, et al. Safety and efficacy of aspirin, clopidogrel, and warfarin after coronary stent placement in patient with an indication for anticoagulation. *Am Heart J*. 2004;147:463-467.
18. Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. *J Invasive Cardiol*. 2006;18:162-164.
19. Rogacka R, Chieffo A, Michev I, et al. Dual antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients taking chronic oral anticoagulation. *JACC Cardiovasc Interv*. 2008;1:56-61.
20. Sambola A, Ferreira-Gonzalez I, Angel J, et al. Therapeutic strategies after coronary stenting in chronically anticoagulated patients: the MUSICA study. *Heart*. 2009;95:1483-1488.
21. Abraham NS, Hartman C, Richardson P, et al. Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. *Circulation*. 2013;128:1869-1877.
22. Rossini R, Musumeci G, Lettieri C, et al. Long term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. *Am J Cardiol*. 2008;102:1618-1623.
23. Gao F, Zhou YJ, Wang ZJ, et al. Comparison of different antithrombotic regimens for patients with atrial fibrillation undergoing drug-eluting stent implantation. *Circ J*. 2010;74:701-770.
24. Wang TY, Robinson LA, Ou FS, et al. Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: physician practice in the CRUSADE registry. *Am Heart J*. 2008;155:361-368.