CLINICAL RESEARCH STUDY

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Safety and Efficacy of Dual Versus Triple Antithrombotic Therapy in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

BACKGROUND: Choosing an antithrombotic regimen after coronary intervention in patients with concomitant indication for anticoagulation is a challenge commonly encountered by clinicians.

METHODS: We performed a meta-analysis of observational studies and randomized, controlled trials comparing outcomes of triple therapy (dual antiplatelet therapy and anticoagulant) with dual therapy (single antiplatelet therapy and anticoagulant) in patients taking long-term anticoagulants after percutaneous coronary intervention. Major bleeding was the primary outcome. Random effects overall risk ratios (RRs) were calculated using the DerSimonian and Laird model.

RESULTS: Nine observational studies and 2 randomized controlled trials with a total of 7276 patients met our selection criteria. At a mean follow-up of 10.8 months major bleeding was higher in the triple therapy cohort compared with dual therapy (6.6% vs 3.8%; RR 1.54; 95% confidence interval [CI], 1.2-1.98; $P < .01$). No difference was observed between the 2 groups for all-cause mortality (RR 0.98; 95% CI, 0.68-1.43; $P = .93$), major adverse cardiac events (RR 1.03; 95% CI, 0.8-1.32; $P = .83$), thromboembolic events (RR 1.02; 95% CI, 0.49-2.10; $P = .96$), myocardial infarction (RR 0.85; 95% CI, 0.67-1.09; $P = .21$), stent thrombosis (RR 0.77; 95% CI, 0.46-1.3; $P = .33$), and target vessel revascularization (RR 0.87; 95% CI, 0.66-1.15; $P = .33$).

CONCLUSION: In patients receiving anticoagulant therapy, a strategy of single antiplatelet therapy confers a benefit of less major bleeding with no difference in all-cause mortality, cardiovascular mortality, major adverse cardiac events, myocardial infarction, stent thrombosis, or thromboembolic event rate compared with dual antiplatelet therapy.

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KEYWORDS: Anticoagulation; Dual therapy; Percutaneous coronary intervention; Triple therapy

Long-term anticoagulation is indicated for most patients with mechanical heart valves, a prior systemic thromboembolic event, and atrial fibrillation/flutter.[1,2] However, in approximately 20%-30% of patients, concomitant ischemic heart disease might be present, requiring percutaneous coronary intervention and stent implantation.[3-5] This would mandate the use of dual antiplatelet therapy (aspirin and an adenosine diphosphate antagonist) for prevention of stent thrombosis and adverse events following percutaneous

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coronary intervention.[6] Thus the patients might require triple therapy consisting of an anticoagulant and dual antiplatelet therapy, which is the current recommendation by both the European Society of Cardiology and the American College of Cardiology guidelines.[1,5] Although the primary intent of triple therapy is to decrease the incidence of major adverse cardiac events, especially stent thrombosis, it has been found to be associated with a high annual risk of bleeding,[7-10] which in turn is strongly associated with recurrent hospitalization and increased morbidity and mortality.[11,12] Recently new evidence has emerged questioning the benefit of triple therapy and suggesting that a regimen of dual therapy with an anticoagulant and a single antiplatelet agent might be equally efficacious to triple therapy, with a lower incidence of major bleeding.[7,13-17] Because the evidence on this topic has mainly been obtained from small observational studies and 2 randomized trials, we performed a systematic review of the literature and meta-analysis to further evaluate the safety and efficacy of both regimens in patients with ischemic heart disease and an indication for anticoagulant after undergoing percutaneous coronary intervention.

CLINICAL SIGNIFICANCE

- For patients with an indication for long-term anticoagulation undergoing coronary stenting, dual therapy is safer than and as effective as triple therapy.
- Major bleeding is less with dual therapy.
- Dual therapy is equivalent to triple therapy in reducing stroke, stent thrombosis, and mortality.

METHODS

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses statement[18] and Meta-analysis Of Observational Studies in Epidemiology[19] were followed during the development of the present systematic review. The protocol of the present meta-analysis was registered at the International Prospective Register for Systematic Reviews or PROSPERO (CRD42016039733).

A search of the electronic databases, including PubMed, Web of Science, and the Cochrane Library database, was conducted from inception until December 2016 for all randomized clinical trials and observational studies comparing triple therapy (defined as an anticoagulant plus dual antiplatelet therapy) with dual therapy (defined as an anticoagulant plus single antiplatelet agent, either aspirin or clopidogrel) in patients undergoing percutaneous coronary intervention. The search was conducted without language restrictions, using the following terms: "dual," "triple," "double," "anticoagulant," "antiplatelet," "clopidogrel," "aspirin," "ticagrelor," "prasugrel," "warfarin," "coronary," "atrial fibrillation," and "percutaneous coronary intervention." References of previous meta-analyses and published studies were reviewed for any studies not included in the main database search; additionally, abstracts of major cardiovascular conferences (for example, American Heart Association, American College of Cardiology, and European Society of Cardiology) were screened for relevant studies.

Two investigators (NA and AJ) assessed the records for eligibility and screened the retrieved records by title and/or abstract. Differences were resolved through consensus between the authors. Included studies met the following criteria: 1) studies comparing dual therapy with triple therapy; 2) patients with an indication for long-term anticoagulation undergoing percutaneous coronary intervention with stenting; 3) clinical follow-up duration no less than 4 weeks; and 4) studies reporting the outcomes of interest. Studies were excluded if they met any of the following criteria: 1) duplicate publication (latest report was selected in that case); 2) ongoing studies or unpublished abstracts; 3) mixed patient population of acute coronary syndrome with and without percutaneous coronary intervention; and 4) nonhuman studies.

Data extraction was performed by the same authors (NA and AJ) independently, which was cross-checked by a third author (RB). The data extracted included information

Table 1 MACE and Major Bleeding Definition

Study	Definition of Major Bleeding	Definition of MACE
Gao et al[20]	TIMI	Death, MI, TVR, CVA, ST
GRACE[21]	GRACE	NR
Karjalanien et al[16]	PRISM-PLUS	Death, MI, TVR, ST
Persson et al[22]	ICD 10 codes	Death, MI
AFCAS[14]	BARC	Death, MI, TVR, CVA, ST
Rubboli et al[23]	ICD 10 codes	CV death, MI, TVR, ST, CVA, VTE
Sambola et al[24]	PRISM-PLUS	CV death, MI, TVR, ST, CVA/PE
De Vecchis et al[15]	ICD 10 codes	Death, ACS, TVR, ST, VTE, CVA
WAR-STENT[25]	TIMI	Death, MI, TVR, CVA, ST, VTE
PIONEER[17]	TIMI	CV death, MI, CVA
WOEST[7]	TIMI/GUSTO/BARC	Death, MI, TVR, CVA, ST

ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; CV = cardiovascular; CVA = cerebrovascular accident; GRACE = Global Registry of Acute Coronary Events; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Artery; ICD = international classification of diseases; MACE = major adverse cardiac event; MI = myocardial infarction; NR = not reported; PE = pulmonary embolism; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization; VTE = venous thromboembolism; WAR-STENT = Warfarin and Coronary Stenting; WOEST = What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting.