Optimal antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: A systemic review and meta-analysis

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Abstract. A challenge for antithrombotic treatment is patients who present with atrial fibrillation (AF) and acute coronary syndrome, particularly in patients who have undergone coronary percutaneous intervention with stenting (PCIS). In the present study, a total of nine observational trials published prior to July 2017 that investigated the effects of dual antiplatelet therapy (DAPT; aspirin + clopidogrel) and triple oral antithrombotic therapy (TOAT; DAPT + warfarin) among patients with AF concurrent to PCIS were collected from the Medline, Cochrane and Embase databases and conference proceedings of cardiology, gastroenterology and neurology meetings. A meta-analysis was performed using fixed- or random- effect models according to heterogeneity. The subgroups were also analyzed on the occurrence of major adverse cardiac events (MACE), stroke and bleeding events in the two treatment groups. Analysis of baseline characteristics indicated that there was no significant difference in the history of coexistent disease or conventional therapies between the DAPT and TOAT groups. The primary end point incidence was 2,588 patients in the DAPT group (n=13,773) and 871 patients in the TOAT group (n=5,262) following pooling of all nine trials. There was no statistically significant difference in the incidence of primary end points between the DAPT and TOAT groups. Odds ratio (OR)=0.96, 95% confidence interval (CI)=0.73-1.27, P=0.79, with heterogeneity between trials (I^2=82%, P<0.00001). Subsequently, on subgroup analysis, the results indicated no increased risk of major bleeding or ischemic stroke in the DAPT or TOAT group. However, compared with the TOAT group, there was an apparent increased risk of MACE plus ischemic stroke in the DAPT group (OR=1.62, 95% CI=1.43-1.83, P<0.00001) with heterogeneity between trials (I^2=70%, P=0.01). In conclusion, the present meta-analysis suggests that TOAT (aspirin + clopidogrel + warfarin) therapy for patients with AF concurrent to PCIS significantly reduced the risk of MACE and stroke compared with DAPT (aspirin + clopidogrel) therapy. Further randomized controlled clinical trials are required to confirm the efficacy of the optimal antithrombotic therapy in patients with AF following PCIS.

Introduction

Stroke prevention is central in the management of patients with atrial fibrillation (AF) (1). The European Society of Cardiology (ESC) guidelines recommend a risk score system, the CHA$_2$DS$_2$-VASc schema, that accounts for congestive heart failure, hypertension, age 65-74 or ≥75 (risk doubled), diabetes, stroke (risk doubled), vascular disease, age and sex (female), to evaluate individual risk of thromboembolism (2,3). Risk assessment should be performed for each case prior to the initiation of antithrombotic therapy to determine the possibility of bleeding and ischemic events. The HAS-BLED scoring system based on hypertension, abnormal renal/liver function, stroke/thromboembolism, bleeding history, labile international normalized ratio (INR), elderly age (>65 years) and drug consumption/alcohol abuse may be used to calculate the risk of bleeding (4-6). This system has been clinically confirmed to accurately predict the risk of thromboembolism and bleeding in patients with AF (2-6).

The majority of patients with AF (70-80%) require continuous oral anticoagulation (OAC) therapy. Additionally, 20-30% patients with AF have comorbid coronary artery disease (CAD) (7-10). Clinicians face a therapeutic challenge in that 5-10% patients undergoing percutaneous coronary intervention with stenting (PCIS) typically require long-term OAC (11-14). Acute coronary syndrome (ACS), incorporating unstable angina/non-ST segment elevation myocardial infarction (MI) and ST-segment elevation MI, constitutes another

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cardiovascular disease type (15). It is associated with risks of mortality and morbidity from MI, heart failure and ventricular arrhythmia (16). Dual antithrombotic treatment consisting of low-dose acetylsalicylic acid and the P2Y12 inhibitors clopidogrel, prasugrel and ticagrelor is a primary strategy for reducing the risk of recurrence of ischemic outcomes, particularly in the first year after acute events (17-19). A particular challenge regarding antithrombotic treatment is patients who present with AF and ACS, particularly as these patients have a high risk of cardiovascular mortality and morbidity (7-15). The present recommendation is triple oral antithrombotic therapy (TOAT; aspirin, clopidogrel and warfarin) for patients with previous MI and/or PCI and concurrent AF, as OAC has been associated with stroke risk factors in patients with AF, while dual antiplatelet therapy (DAPT; aspirin and clopidogrel) has been associated with ACS following PCI (20). However, the prevalence of major bleeding with triple therapy increases with treatment duration (21-22).

To date, there is a lack of randomized studies comparing the safety and efficacy of the antithrombotic regimens TOAT and DAPT. The nine observational trials included in the current meta-analysis had the inherent limitations of a nonrandomized study design; however, the meta-analysis was feasible as the grouping criteria were similar. The primary end points of DAPT and triple therapy among patients with AF concurrent to PCIS were evaluated, and subgroup analysis of major adverse cardiac events (MACE), stroke and bleeding events was performed to compare the treatment strategies. This aimed to provide a basis for rational clinical decisions on the optimal treatment for individual patients with AF concurrent to PCIS.

Materials and methods

Eligibility criteria. The search strategy focused on observational studies in which patients were receiving DAPT (clopidogrel + aspirin) classified into those with concomitant warfarin treatment or non-warfarin users. The outcomes of interest were MACE (defined as death, ACS, stent thrombosis, revascularization and nonfatal MI), ischemic stroke, major bleedings and minor bleedings (23-31). Major bleeding was defined as severe or moderate bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries criteria (25). Minor bleeding was defined as any clinically overt sign of bleeding associated with a decrease in hemoglobin between 3 and 5 g/l (32). Reviews, letters, comments, nonclinical investigations, articles with data on platelet activity only or no relevant data and article published in languages other than Chinese or English were excluded.

Search strategy and selection criteria. A comprehensive search was performed for studies published prior to July 7, 2017 that focused on TOAT or DAPT antithrombotic therapy and evaluated the outcomes of the different strategies in patients with atrial fibrillation (AF) receiving PCIS. Searches were performed on Medline (http://www.nlm.nih.gov/bsd/pmresources.html), Embase (https://www.elsevier.com/solutions/embase-biomedical-research), Cochrane (http://uk.cochrane.org/) and the Chinese Biomedical Literature Database (CBM; http://www.sinomed.ac.cn/).

Data sources and searches. Electronic searches were performed using the search terms 'AF', 'clopidogrel', 'Plavix', 'aspirin', 'warfarin', 'TOAT', 'DAPT', and 'PCIS'. Searches were conducted according to the characteristics of each database. Bibliographies from included articles and review articles were hand-searched, and cardiovascular research professionals were consulted to ensure inclusion of all pertinent studies.

Study selection. Two reviewers independently screened the abstracts and titles of the studies from the electronic search to identify all potential eligible studies. Potential relevant literatures were then retrieved as full-text manuscripts for further assessment of eligibility. Any discrepancies or uncertainties between the reviewers were resolved by consultation or consensus with a third reviewer. The authors were also contacted if any areas of uncertainty required clarification.

Data extraction. Two investigators independently extracted data on patient and study characteristics, exposure factors, outcomes and study quality for each study using a standard data extraction form (33). Consensus with the third reviewer resolved any discrepancies. The following information was extracted from each study: First author, year of publication, location, study design and number of patients, mean age (and standard deviation), sex, underlying disease, type of anti-thrombosis drug used (TOAT or DAPT), duration of follow-up, outcomes, analyzed effect, odds ratio (OR) and adjusted variables.

Data analysis. Extracted information from included studies was entered into a table to assess the study subjects, exposure factors, outcomes, quality and design of each study and the heterogeneity of included studies. ORs with 95% confidence intervals (CIs) were determined for binary outcomes. Statistical heterogeneity was assessed using the χ^2 test and was quantified using the I^2 statistic. When there was significant heterogeneity with $P<0.1$, a random-effects model was used via the DerSimonian and Laird method; otherwise, a fixed-effects model was used via the Mantel-Haenszel method. The clinical outcomes of patients with AF following percutaneous intervention and treatment with different oral antithrombotic therapies (TOAT or DAPT) were evaluated. The Mantel-Haenszel method was used to calculate the ORs for clinical outcomes between the DAPT and TOAT groups. For meta-regression, sensitivity analyses of primary outcomes were conducted after eliminating the maximum and minimum of effect size to determine the stability of results. Finally, small study bias and/or publication bias was assessed by visual inspection of a funnel plot and Egger's test. Additionally, the Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies in meta-analyses was used (34), which is based on three domains: Selection of study groups, comparability of groups and ascertainment of exposure/outcome.

Results

Description of the studies. A total of nine observational trials were included in the present study, consisting of 19,035 patients in total (23-31). The flow of included studies through the selection process is depicted showed in Fig. 1. The baseline

Table I. Design and baseline characteristics of the selected studies.

Author, year	DAPT		TOAT		Clinical outcome	Median, follow-up years	CHA$_2$DS$_2$ VASc score patients,(%)	Refs.
	Events, no.	Total patients, no.	Events, no.	Total patients, no.				
Choi et al, 2017	112	629	16	75	The primary outcome was a composite of cardiovascular mortality, non fatal MI or nonfatal stroke (from any cause). The principal secondary outcomes were mortality (from any cause, cardiovascular or non-cardiovascular), MI, stroke (from any cause, ischemic or hemorrhage), stent thrombosis, repeat revascularization and bleeding (major or nonmajor).	6.2	DAPT: ≥2 (71.1) TOAT: ≥2 (73.3)	(23)
Lamberts et al, 2012	725	3,144	269	1,495	The primary outcome was nonfatal or fatal bleeding. The secondary outcomes were, ischemic stroke nonfatal MI or nonfatal ischemic stroke.	8.0	DAPT: ≥2 (56.5) TOAT: ≥2 (60.8)	(24)
Kang et al, 2015	42	236	29	131	The primary end point was a 2-year net clinical outcome: A composite of major bleeding and major adverse cardiac and cerebral events.	2.0	DAPT: ≥2 (76.6) TOAT: ≥2 (90.0)	(25)
Gao et al, 2010	67	334	12	136	The primary end point was defined as the occurrence of MACE, including mortality, MI, target vessel revascularization, stent thrombosis or stroke at 12 months. Secondary safety end points were major or minor bleeding complications during the follow-up period.	1.0	CHADS$_2$ score ≥2 (45.8)	(26)
Fosbol et al, 2012	922	2,841	187	731	The primary outcome was a major cardiac event within 1 year defined as a composite end point of mortality, hospitalization for recurrent MI or hospital for ischemic stroke. The second outcome was 1-year hospitalization for bleeding, intracranial hemorrhage, hemarthrosis, hemopericardium, unspecified hemorrhage or acute posthemorrhagic anemia.	1.0	n/a	(27)
Manzano-Fernandez et al, 2008	0	38	2	49	The primary end point was defined as the occurence of major bleeding complications (fatal bleeding, a decrease in the blood hemoglobin level >4g/l, need for transfusion of ≥2 U blood, need for corrective	1.0	n/a	(28)

Table I. Continued.

Author, year	DAPT		TOAT		Clinical outcome	Median, follow-up years	CHA$_2$DS$_2$-VASc score (patients, %)	Refs.
	Events, no.	Total patients, no.	Events, no.	Total patients, no.				
					surgical intervention, the occurrence of intracranial or retroperitoneal bleeding or any combination of these events. The secondary end points were cardiovascular mortality, myocardial infarction, need of new revascularization, stent thrombosis, or thromboembolic complications (MACE).			
Maegdefessel *et al*, 2008	18	103	1	14	A combined end point comprised of severe bleeding events, myocardial infarctions, strokes and cardiovascular death.	1.4	n/a	(29)
Hansen *et al*, 2010	94	2,859	64	1,261	The primary end point was bleeding. Bleeding was defined as an admission to a Danish hospital with a bleeding diagnosis (primary or secondary), a nonfatal bleeding episode or a diagnosis of bleeding as a cause of mortality. The second end points were ischemic stroke, defined as nonfatal ischemic or unspecified stroke diagnosis.	3.3	n/a	(30)
Hess *et al*, 2015	1,173	3,589	446	1,370	The primary outcome was 2-year MACE comprising of mortality, readmission for MI or stroke. Secondary effectiveness outcomes included individual components of composite MACE, as well as ischemic stroke alone.	2.0	n/a	(31)

MACE, major adverse cardiovascular events; n/a, not available.

and design characteristics of the selected studies are listed in Table I. The range of participant number was 87-4,959, including men and women (1.6:1 ratio). The effects of DAPT and TOAT among these patients with AF concurrent to PCIS were compared.

Quality assessment of the trials and publication bias. According to the Newcastle-Ottawa Scale assessment, the selected trials in the meta-analysis were well-designed and reasonably conducted. Publication bias was assessed by Egger's test as depicted in Fig. 2. The funnel plot was not markedly skewed, indicating the absence of publication bias in the meta-analysis.

Effect of antithrombotic therapy on primary end point, MACE, ischemic stroke and major bleeding events. Analysis of baseline characteristics indicated no significant in the history of co-existent disease or conventional therapies between the DAPT and TOAT groups. The primary end point incidence was 2,588 patients in the DAPT group (n=13,773) and 871 patients in the TOAT group (n=5,262) on pooling of all nine trials. There was no statistically significant difference
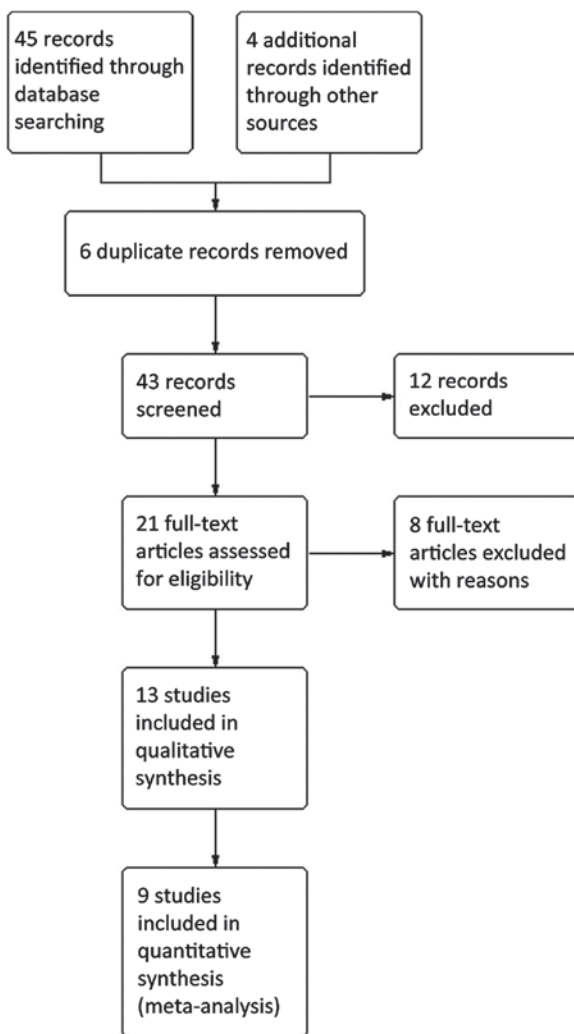
Figure 1. Flow of included studies through the selection process. A total of nine observational trials involving 19,035 patients were included in the meta-analysis.
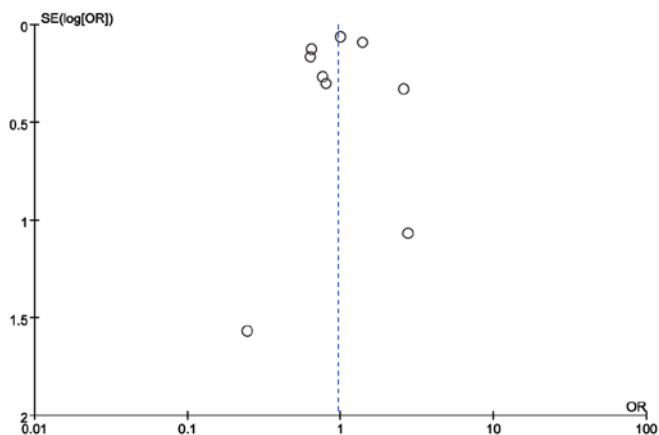

Figure 2. Publication bias assessed by Egger's test. SE, standard error; OR, odds ratio.

in the incidence of primary end points between the groups (OR=0.96, 95% CI=0.73-1.27, P=0.79; Fig. 3) with heterogeneity between trials (I^2=82%, P<0.00001).

This high heterogeneity in the nine trials (I^2=82%, P<0.00001) may be due to differing definitions of the primary end point. The primary end points of Choi *et al* (23), Kang *et al* (25), Gao *et al* (26), Fosbol *et al* (27) and Hess *et al* (31) were generally nonfatal MI, cardiovascular mortality and nonfatal stroke. By contrast, the primary end point of Lamberts *et al* (24), Manzano-Fernández *et al* (28), Maegdefessel *et al* (29) and Hansen *et al* (30) was fatal or nonfatal bleeding.

The data of Choi et al (23), Lamberts *et al* (24), Gao *et al* (26), Fosbol *et al* (27), and Manzano-Fernández *et al* (28) were pooled for subgroup analysis in order to compare the incidence of MACE plus ischemic stroke in the DAPT and TOAT groups. An increased risk of MACE plus ischemic stroke was identified in the DAPT group compared with the TOAT group among patients with AF concurrent to PCIS (OR=1.62, 95% CI=1.43-1.83, P<0.00001) with heterogeneity between the trials (I^2=70%, P=0.01; Fig. 4).

Furthermore, data regarding major bleeding events in the nine studies were pooled to compare the incidence of major bleeding between the DAPT and TOAT groups. No increased risk of major bleeding was observed in the DAPT or TOAT group (OR=0.94, 95% CI=0.84-1.06, P=0.32; Fig. 5). However, there was significant heterogeneity among the nine studies (I^2=84%, P<0.00001).

Data regarding ischemic stroke in Choi *et al* (23), Kang *et al* (25), Gao *et al* (26), Fosbol *et al* (27), Maegdefessel *et al* (29) and Hess *et al* (31) were also pooled to compare the incidence of ischemic stroke between the DAPT and TOAT groups. No increased risk of ischemic stroke was identified in the DAPT group compared with the TOAT group among patients with AF concurrent to PCIS (OR=1.23, 95% CI=0.96-1.58, P=0.11; Fig. 6) with no significant heterogeneity between the trials (I^2=14%, P=0.33).

Discussion

In the present meta-analysis, nine observational trials were pooled to determine the optimal antithrombotic strategy in patients with AF following PCIS. On comparing DAPT (aspirin and clopidogrel) with TOAT (aspirin + clopidogrel + warfarin), the results indicated that neither TOAT nor DAPT were associated with an increased incidence of primary end point, major bleeding or ischemic stroke in patients with AF following percutaneous intervention. However, there was an increased incidence of MACE plus stroke in AF patients treated with DAPT when compared with the TOAT group.

AF is a common cardiac arrhythmia, particularly in older individuals (35), with a prevalence of approximately 10% in patients above 80 years old (36). It is established that AF is an independent risk factor for stroke (37). In the presence of other risk factors of cardiovascular disease, the occurrence of stroke due to AF ranges from 2 to 18% (38). The ESC guidelines have recommended the use of the CHA_2DS_2-VASc score for stroke risk assessment and define 'low-risk' patients as those with a CHA_2DS_2-VASC score of 0 (males) or ≤1 (females) (39). Furthermore, scores of HAS-BLED may be used to calculate the risk of bleeding (35,39,40). These scores have been clinically confirmed to accurately predict the risk of thromboembolism and bleeding in AF patients (2-6). Among the different oral antithrombotic therapies studied,
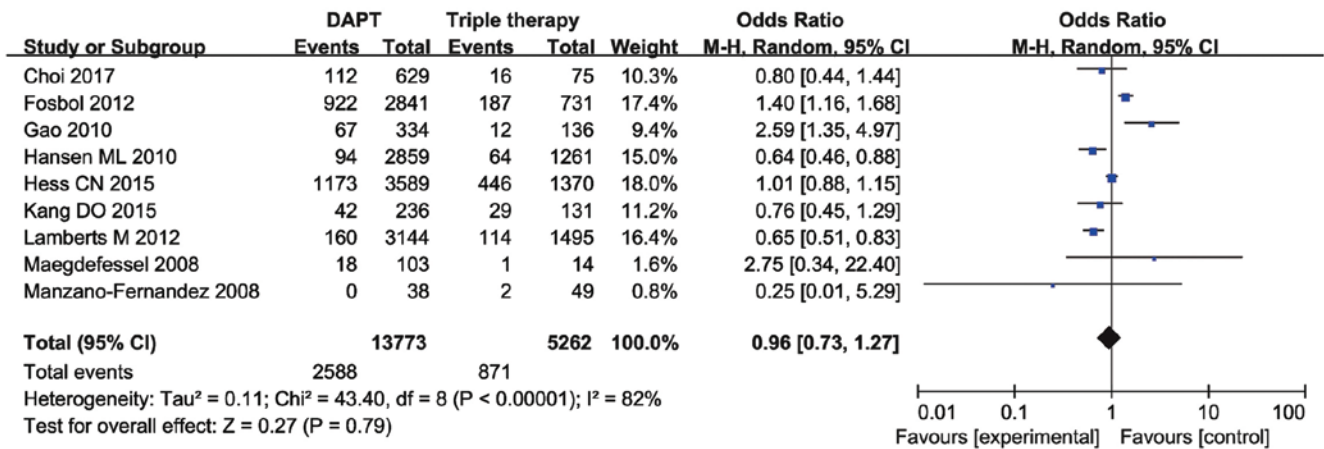
Figure 3. Forest plot showing relative risk of the primary end point incidence. Primary end point incidence was 2,588 patients in the DAPT group (n=13,773) and 871 patients in the TOAT group (n=5,262) on pooling all nine trials. There was no statistically significant difference in primary end point incidence (OR=0.96, 95% CI=0.73-1.27, P=0.79.) with heterogeneity between trials (I^2=82%, P<0.00001). The M-H method was used to estimate the pooled OR for all strata. DAPT, dual antiplatelet therapy; TOAT, triple oral antithrombotic therapy; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel.
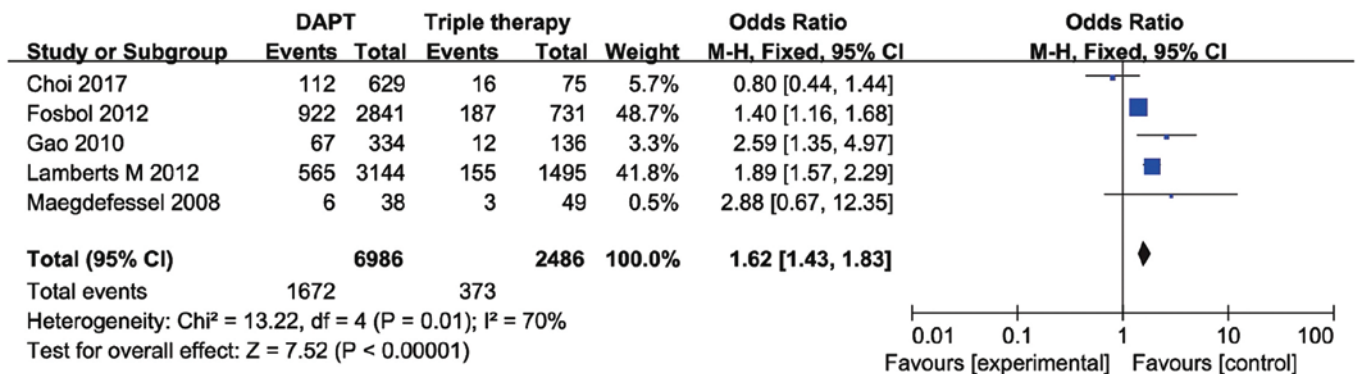

Figure 4. Forest plot showing relative risk of MACE and ischemic stroke. An increased risk of MACE and ischemic stroke was identified in the DAPT group compared with the TOAT group among patients with atrial fibrillation concurrent to percutaneous coronary intervention with stenting (OR=1.62, 95% CI=1.43-1.83, P<0.00001) with heterogeneity between trials (I^2=70%, P=0.01). MACE, major adverse cardiovascular events; DAPT, dual antiplatelet therapy; TOAT, triple oral antithrombotic therapy; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel method.
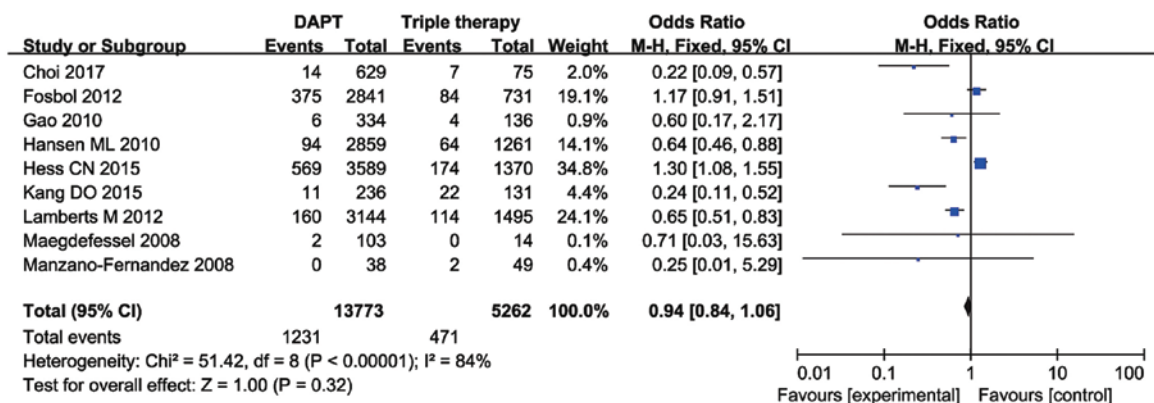

Figure 5. Forest plot showing relative risk of major bleeding events. There was no increased risk of major bleeding in the DAPT group compared with the TOAT group among patients with atrial fibrillation concurrent to percutaneous coronary intervention with stenting (OR=0.94, 95% CI=0.84-1.06, P=0.32.). There was statistical heterogeneity among the nine included studies (I^2=84%, P<0.00001). DAPT, dual antiplatelet therapy; TOAT, triple oral antithrombotic therapy; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel method.

warfarin has been demonstrated to reduce stroke risk by 64% when compared with placebo and by 39% when compared with aspirin in patients with AF (41). Furthermore, TOAT has been demonstrated to have greater efficiency than DAPT when tested as an alternative antithrombotic treatment (23-31).

Study or Subgroup	DAPT Events	Total	Triple therapy Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
3.1.2 DAPT VS TRIPLE (ischemic stroke)							
Choi 2017	50	629	7	75	10.1%	0.84 [0.37, 1.92]	
Fosbol 2012	45	2842	5	731	6.9%	2.34 [0.92, 5.91]	
Gao 2010	12	334	1	136	1.2%	5.03 [0.65, 39.08]	
Hess CN 2015	190	3589	64	1370	76.8%	1.14 [0.85, 1.53]	
Kang DO 2015	5	236	4	131	4.4%	0.69 [0.18, 2.60]	
Maegdefessel 2008	9	103	0	14	0.7%	2.92 [0.16, 52.83]	
Subtotal (95% CI)		7733		2457	100.0%	1.23 [0.96, 1.58]	
Total events	311		81				

Heterogeneity: Chi² = 5.81, df = 5 (P = 0.33); I² = 14%
Test for overall effect: Z = 1.62 (P = 0.11)

Total (95% CI)		7733		2457	100.0%	1.23 [0.96, 1.58]	
Total events	311		81				

Heterogeneity: Chi² = 5.81, df = 5 (P = 0.33); I² = 14%
Test for overall effect: Z = 1.62 (P = 0.11)
Test for subgroup differences: Not applicable

0.01   0.1   1   10   100
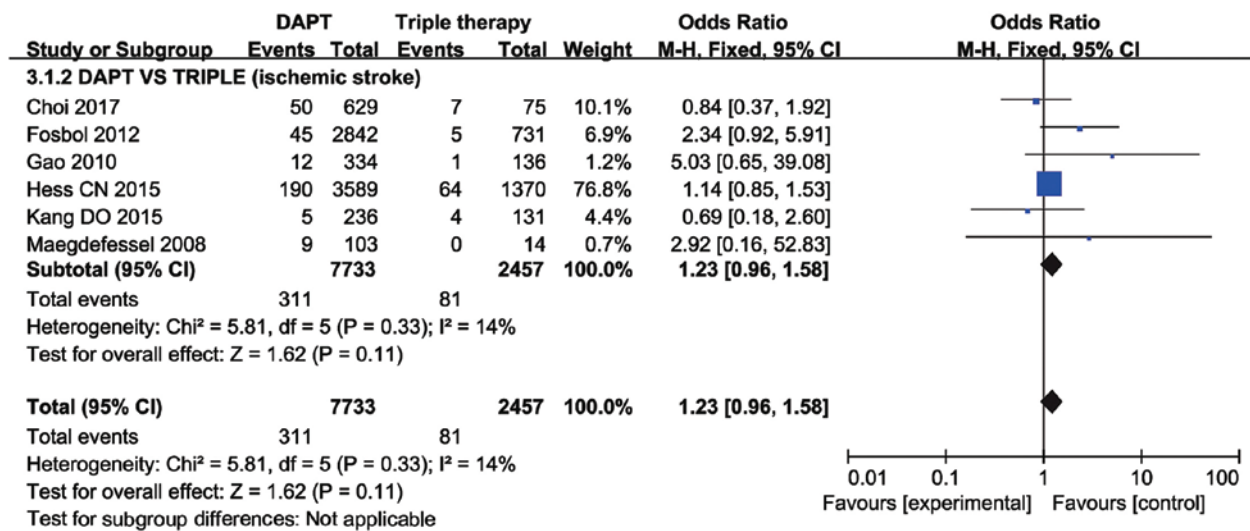Favours [experimental]   Favours [control]

Figure 6. Forest plot showing relative risk of ischemic stroke. There was no increased risk of ischemic stroke in the DAPT group compared with the TOAT group among patients with atrial fibrillation concurrent to percutaneous coronary intervention with stenting (OR=1.23, 95% CI=0.96-1.58, P=0.11) with no significant heterogeneity between the trials (I²=14%, P=0.33). DAPT, dual antiplatelet therapy; TOAT, triple oral antithrombotic therapy; OR, odds ratio; CI, confidence interval; M-H, Mantel-Haenszel method.

Since 2001, the standard antithrombotic strategy has been DAPT therapy with aspirin plus clopidogrel for patients with ACS and for patients undergoing PCIS, in order to prevent complications including stent thrombosis, recurrent MI and stroke (42-45). Although aspirin is established to significantly reduce cardiovascular events in ACS, concurrent clopidogrel as a second antiplatelet has been demonstrated to significantly improve ACS outcomes compared with aspirin alone. Previously, other antiplatelet agents (prasugrel or ticagrelor) have been clinically used as substitutions for clopidogrel in the occurrence of ACS; these agents have been reported to achieve a higher degree inhibition of platelet aggregation compared with clopidogrel and do not seem to be affected by CYP2C19 polymorphism (18,46). Additionally, a previous study reported improved clinical outcomes of patients with ACS following treatment with prasugrel or ticagrelor compared with clopidogrel, though this was accompanied by an increase in bleeding risk, particularly in those undergoing PCI (46). The use of DAPT has been recommended by recent European guidelines for at least four weeks following bare-metal stenting and for at least six months following drug-eluting stenting (35,47). The majority of patients with AF (70-80%) require continuous OAC, and CAD develops in 20-30% of these patients (7-10). Clinicians are faced with a therapeutic challenge in that 5-10% patients undergoing PCIS typically require long-term OAC therapy (11-14). A particular challenge in antithrombotic therapy is patients who present with both AF and ACS (7-14). There is a slight difference in the pathogenesis of thrombi development between patients with AF or CAD: The type of thrombi in patients with CAD is platelet-rich, while thrombi in AF patients is fibrin-rich (48-50). Compared with OAC alone, combined aspirin and clopidogrel therapy is less effective in preventing stroke in patients with AF following PCIS; however OAC alone is insufficient for preventing stent thrombosis. TOAT is typically necessary to prevent ischemic stroke, MI or stent thrombosis associated with PCIS or ACS in patients with comorbid CAD

and AF (48). TOAT can completely prevent these thrombotic complications, though at the expense of increased bleeding risk (49,50). Future studies should aim to provide safety and efficacy data for guiding clinical practice, to overcome the challenge of determining the optimal antithrombotic treatment for patients. Optimal treatments may include: Omitting aspirin, reducing TOAT duration, exchanging warfarin for a direct OAC (DOAC), the use of DOAC in combination with a single antiplatelet agent, exchanging clopidogrel for a novel antiplatelet agent, and DAPT (51,52). The omission of clopidogrel in patients receiving coronary stents has been associated with an increased risk of thrombotic outcomes, including MI and stent thrombosis (42,43). Although omitting aspirin and reducing TOAT duration may be effective in selected AF patients with a low risk of thrombosis, the role of DOACs and novel antiplatelet agents in TOAT is yet to be determined, and there is limited data to support their use at present (23-31). To date, there has been a lack of randomized studies comparing the safety and efficacy of TOAT and classical DAPT. Meta-analyses of observational studies have the potential to provide clinically useful data on adverse event rates of a given therapy and in comparison with other treatments. The nine trials included in the present study had all the inherent limitations of a nonrandomized study design; however, the meta-analysis was very feasible as the grouping standards were similar. In patients with AF, triple therapy was not associated with decreased primary end point events, stroke or major bleeding, though was associated with decreased MACE and stroke incidence, compared with DAPT.

Gao *et al* (53) previously assessed patients with indications of chronic OAC, and confirmed the cardiovascular benefits of triple antithrombotic therapy through reducing ischemic stroke risk, though also demonstrated an increased risk of major bleeding. A meta-analysis by Zhao *et al* (54) included nine clinical trials, and identified that triple antithrombotic treatment was adequate and more efficient in reducing the occurrence of cardiovascular events and mortality in PCIS

patients potentially requiring long-term OAC compared with DAPT. Although these previous meta-analyses combined several studies and reported significant differences in the occurrence of MACE or ischemic stroke in patients receiving different antithrombotic treatments, results were limited as less than 5,200 participants were included in each. Additionally, patients with conditions other than AF, including mechanical prosthetic heart valves, deep venous thrombosis, left ventricular thrombus and pulmonary embolism, were also included (53,55). Saheb et al (55) performed a meta-analysis of triple antithrombotic therapy compared with DAPT following PCI with implantation in patients requiring chronic OAC therapy. They identified that the occurrence of ischemic stroke in PCIS patients potentially requiring chronic OAC was more effectively reduced by triple therapy compared with DAPT. However, the patients were not solely confined to individuals with AF and CHADS$_2$>1 (6), but also those with mechanical prosthetic heart valves, deep venous thrombosis, left ventricular thrombus or pulmonary embolism (55). Andrade et al (56) performed a meta-analysis of observational trials concerning triple antithrombotic therapy following PCIS. They concluded that the rate of major bleeding associated with TOAT was clinically significant and higher than that for DAPT. However, the meta-analysis included patients with left ventricular mural thrombus, pulmonary embolism, venous or systematic thromboembolism or ACS along with AF subjects undergoing PCIS (56). Previous results have demonstrated that patients receiving triple antiplatelet therapy with an INR within the lower therapeutic range (2.0-2.5), as the recommended target, had a severe bleeding risk compared with patients receiving dual therapy only (55). Conversely, the lower INR was effective in preventing ischemic complications, demonstrated by low MACE rate at long-term follow-up (55). However, these results are not applicable to patients with mechanical valve prostheses, who typically present with higher INR values (54-56).

The present meta-analysis included only patients with AF concurrent to PCIS who had undergone TOAT or DAPT. The results suggested that TOAT reduced the occurrence of MACE and ischemic stroke in the AF patients, potentially due to the following factors: i) The type of thrombus in AF is mainly fibrin-rich, and thus platelets serve a smaller role, enabling OAC to have a more efficient prophylactic effect compared with antiplatelet therapy for stroke prevention; and ii) anticoagulation reduces the occurrence of thrombosis in chambers of the heart or other locations to lower the rate of embolism events in the coronary artery (48-50). Large-scale, randomized, prospective and multicenter studies are now required to confirm the optimal therapeutic strategy for patients with AF undergoing coronary stenting.

The current meta-analysis had several limitations. Many studies were implicated to have risk of bias. The heterogeneity may partly be due to the variability in the definition of clinical outcomes across studies. Information was also lacking on the baseline characteristics of participants regarding key variables including left ventricular ejection fraction, smoking, body mass index, use of implantable defibrillators and function of the CYP2C19 allele, which may have been important confounders. Instead, much of the data were from computerized data-bases,

which may not record or classify accurate information on study outcomes and exposures.

For future studies, a standardized individual cardiovascular outcome should be defined based on hard end points including MI, mortality, stroke and hemorrhage, despite the ease of applying composite results with higher event rates. However, a large-scale randomized controlled trial with broad rather than restrictive selection criteria may be more useful for clinical practice. Thus, well-designed, randomized trials are now required to assess the optimal antithrombotic treatments in patients with AF following PCI.

In conclusion, the current meta-analysis of nine observational trials indicated that TOAT for patients with AF concurrent to PCIS significantly reduced the risk of MACE and stroke when compared with DAPT. To date, trials are too inconsistent to establish a conclusion on the efficacy of dual and triple therapy. Therefore, further randomized clinical controlled trials are required to confirm the efficacy of the optimal antithrombotic therapy in patients with AF following PCIS.

Acknowledgements

References

1. Kanagaratnam L, Kowey P and Whalley D: Pharmacological therapy for rate and rhythm control for atrial fibrillation in 2017. Heart Lung Circ 26: 926-933, 2017.
2. Boriani G, Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Ricci R, Biffi M, De Santo T, Corbucci G, et al: Italian AT-500 registry investigators: Improving stroke risk stratification using the CHADS2 and CHA2DS2-VASc risk scores in patients with paroxysmal atrial fibrillation by continuous arrhythmia burden monitoring. Stroke 42: 1768-1770, 2011.
3. Mazurek M, Shantsila E, Lane DA, Wolff A, Proietti M and Lip GYH: Guideline-adherent antithrombotic treatment improves outcomes in patients with atrial fibrillation: Insights from the community-based Darlington atrial fibrillation registry. Mayo Clin Proc 92: 1203-1213, 2017.
4. Koene RJ, Win S, Naksuk N, Adatya SN, Rosenbaum AN, John R and Eckman PM: HAS-BLED and CHA$_2$DS$_2$-VASc scores as predictors of bleeding and thrombotic risk after continuous-flow ventricular assist device implantation. J Card Fail 20: 800-807, 2014.
5. Roldán V, Marín F, Manzano-Fernández S, Gallego P, Vílchez JA, Valdés M, Vicente V and Lip GY: The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. J Am Coll Cardiol 62: 2199-2204, 2013.
6. Apostolakis S, Lane DA, Buller H and Lip GY: Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: The AMADEUS trial. Thromb Haemost 110: 1074-1079, 2013.

7. Angiolillo DJ, Goodman SG, Bhatt DL, Eikelboom JW, Price MJ, Moliterno DJ, Cannon CP, Tanguay JF, Granger CB, Mauri L, et al: Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: A North American Perspective-2016 Update. Circ Cardiovasc Interv 9: 9, 2016.

8. Kralev S, Schneider K, Lang S, Süselbeck T and Borggrefe M: Incidence and severity of coronary artery disease in patients with atrial fibrillation undergoing first-time coronary angiography. PLoS One 6: e24964, 2011.

9. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, et al; European Heart Survey Investigators: Atrial fibrillation management: A prospective survey in ESC member countries: The Euro Heart Survey on Atrial Fibrillation. Eur Heart J 26: 2422-2434, 2005.

10. Nabauer M, Gerth A, Limbourg T, Schneider S, Oeff M, Kirchhof P, Goette A, Lewalter T, Ravens U, Meinertz T, et al: The registry of the German competence NETwork on atrial fibrillation: Patient characteristics and initial management. Europace 11: 423-434, 2009.

11. Rossini R, Musumeci G, Lettieri C, Molfese M, Mihalcsik L, Mantovani P, Sirbu V, Bass TA, Della Rovere F, Gavazzi A, et al: Long-term outcomes in patients undergoing coronary stenting on dual oral antiplatelet treatment requiring oral anticoagulant therapy. Am J Cardiol 102: 1618-1623, 2008.

12. Wang TY, Robinson LA, Ou FS, Roe MT, Ohman EM, Gibler WB, Smith SC Jr, Peterson ED and Becker RC: Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: Physician practice in the CRUSADE registry. Am Heart J 155: 361-368, 2008.

13. Rubboli A, Colletta M, Valencia J, Capecchi A, Franco N, Zanolla L, La Vecchia L, Piovaccari G and Di Pasquale G; WARfarin and Coronary STENTing (WAR-STENT) study group: Periprocedural management and in-hospital outcome of patients with indication for oral anticoagulation undergoing coronary artery stenting. J Interv Cardiol 22: 390-397, 2009.

14. Capodanno D and Angiolillo DJ: Management of antiplatelet and anticoagulant therapy in patients with atrial fibrillation in the setting of acute coronary syndromes or percutaneous coronary interventions. Circ Cardiovasc Interv 7: 113-124, 2014.

15. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ et al: 2014 ESC/EACTS guidelines on myocardial revascularization: The task force on myocardial revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 35: 2541-2619, 2014.

16. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüniet P, et al: 2014 ESC/EACTS guidelines on myocardial revascularization. Rev Esp Cardiol 68: 452, 2015.

17. Gurbel PA, Bliden KP, Hiatt BL and O'Connor CM: Clopidogrel for coronary stenting: Response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 107: 2908-2913, 2003.

18. James SK, Roe MT, Cannon CP, Cornel JH, Horrow J, Husted S, Katus H, Morais J, Steg PG, Storey RF, et al; PLATO Study Group: Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: Substudy from prospective randomised PLATelet inhibition and patient outcomes (PLATO) trial. BMJ 342: 3527, 2011.

19. Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, Harrington RA, Horrow J, Husted S, James SK, et al: Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: Results from the PLATO (Platelet Inhibition and Patient Outcomes) trial. J Am Coll Cardiol 57: 672-684, 2011.

20. Gwyn JCV, Thomas MR and Kirchhof P: Triple antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: A viewpoint. Eur Heart J Cardiovasc Pharmacother 3: 157-162, 2017.

21. Lopes RD, Rao M, Simon DN, Thomas L, Ansell J, Fonarow GC, Gersh BJ, Go AS, Hylek EM, Kowey P, et al: Triple vs dual antithrombotic therapy in patients with atrial fibrillation and coronary artery disease. Am J Med 129: 592-599, 2016.

22. Pareek M, Bhatt DL, Ten Berg JM, Kristensen SD and Grove EL: Antithrombotic strategies for preventing long-term major adverse cardiovascular events in patients with non-valvular atrial fibrillation who undergo percutaneous coronary intervention. Expert Opin Pharmacother 18: 875-883, 2017.

23. Choi HI, Ahn JM, Kang SH, Lee PH, Kang SJ, Lee SW, Kim YH, Lee CW, Park SW, Park DW, et al: Prevalence, management, and long-term (6-year) outcomes of atrial fibrillation among patients receiving drug-eluting coronary stents. JACC Cardiovasc Interv 10: 1075-1085, 2017.

24. Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, Køber L, Torp-Pedersen C, Gislason GH and Hansen ML: Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: A nationwide cohort study. Circulation 126: 1185-1193, 2012.

25. Kang DO, Yu CW, Kim HD, Cho JY, Joo HJ, Choi RK, Park JS, Lee HJ, Kim JS, Park JH, et al: Triple antithrombotic therapy versus dual antiplatelet therapy in patients with atrial fibrillation undergoing drug-eluting stent implantation. Coron Artery Dis 26: 372-380, 2015.

26. Gao F, Zhou YJ, Wang ZJ, Shen H, Liu XL, Nie B, Yan ZX, Yang SW, Jia de A and Yu M: Comparison of different antithrombotic regimens for patients with atrial fibrillation undergoing drug-eluting stent implantation. Circ J 74: 701-708, 2010.

27. Fosbol EL, Wang TY, Li S, Piccini JP, Lopes RD, Shah B, Mills RM, Klaskala W, Alexander KP, Thomas L, et al: Safety and effectiveness of antithrombotic strategies in older adult patients with atrial fibrillation and non-ST elevation myocardial infarction. Am Heart J 163: 720-728, 2012.

28. Manzano-Fernández S, Pastor FJ, Marín F, Cambronero F, Caro C, Pascual-Figal DA, Garrido IP, Pinar E, Valdés M and Lip GYH: Increased major bleeding complications related to triple antithrombotic therapy usage in patients with atrial fibrillation undergoing percutaneous coronary artery stenting. Chest 134: 559-567, 2008.

29. Maegdefessel L, Schlitt A, Faerber J, Bond SP, Messow CM, Buerke M, Raaz U, Werdan K, Muenzel T, and Weiss C: Anticoagulant and/or antiplatelet treatment in patients with atrial fibrillation after percutaneous coronary intervention. A single-center experience. Med Klin (Munich) 103: 628-632, 2008.

30. Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N, Gislason GH, Folke F, Andersen SS, Schramm TK, et al: Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med 170: 1433-1441, 2010.

31. Hess CN, Peterson ED, Peng SA, de Lemos JA, Fosbol EL, Thomas L, Bhatt DL, Saucedo JF and Wang TY: Use and outcomes of triple therapy among older patients with acute myocardial infarction and atrial fibrillation. J Am Coll Cardiol 66: 616-627, 2015.

32. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL and Terrin ML: Thrombolysis in Myocardial Infarction (TIMI) Trial-phase I: Hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 11: 1-11, 1988.

33. Li JX, Jin EZ, Yu LH, Li Y, Liu NN, Dong YM, Li X and Li XQ: Oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients following coronary angioplasty: A meta-analysis. Exp Ther Med 14: 1568-1576, 2017.

34. Stang A: Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25: 603-605, 2010.

35. Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, et al; Document reviewers: Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: A joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J 35: 3155-3179, 2014.

36. JCS Joint Working Group: Guidelines for pharmacotherapy of atrial fibrillation (JCS 2013). Circ J 78: 1997-2021, 2014.

37. Heidenreich PA, Solis P, Estes NA III, Fonarow GC, Jurgens CY, Marine JE, McManus DD and McNamara RL: 2016 ACC/AHA Clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: A report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol 68: 525-568, 2016.
38. Elewa H, Ahmed D and Barnes GD: Triple oral antithrombotic therapy in atrial fibrillation and coronary artery stenting: Searching for the best combination. Semin Thromb Hemost 42: 662-670, 2016.
39. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, *et al*; European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery: Guidelines for the management of atrial fibrillation: The Task Force for the management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 31: 2369-2429, 2010.
40. Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL, Weiss TW, Collet JP, Andreotti F, Gulba DC, *et al*; ESC Working Group on Thrombosis: Management of antithrombotic therapy after bleeding in patients with coronary artery disease and/or atrial fibrillation: Expert consensus paper of the European Society of Cardiology working group on thrombosis. Eur Heart J 38: 1455-1462, 2017.
41. Hart RG, Pearce LA and Aguilar MI: Meta-analysis: Antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 146: 857-867, 2007.
42. Peters RJ, Mehta SR, Fox KA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V and Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial Investigators: Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: Observations from the clopidogrel in unstable angina to prevent recurrent events (CURE) study. Circulation 108: 1682-1687, 2003.
43. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, Lewis BS, Murphy SA, McCabe CH and Braunwald E; Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 Investigators: Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: The PCI-CLARITY study. JAMA 294: 1224-1232, 2005.
44. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, *et al*; Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI): Guidelines on myocardial revascularization. Eur Heart J 31: 2501-2555, 2010.
45. Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, Husted S, Katus H, Steg PG, Shah SH, *et al*: Effect of CYP2C19 and ABCB1 single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: A genetic substudy of the PLATO trial. Lancet 376: 1320-1328, 2010.
46. Khayata M, Gabra JN, Nasser MF, Litman GI, Bhakta S and Raina R: Comparison of clopidogrel with prasugrel and ticagrelor in patients with acute coronary syndrome: Clinical outcomes from the national cardiovascular database ACTION registry. Cardiol Res 8: 105-110, 2017.
47. O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, *et al*; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions: 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 61: e78-e140, 2013.
48. Reed GW and Cannon CP: Triple oral antithrombotic therapy in atrial fibrillation and coronary artery stenting. Clin Cardiol 36: 585-594, 2013.
49. Dzeshka MS, Brown RA and Lip GY: Patients with atrial fibrillation undergoing percutaneous coronary intervention. Current concepts and concerns: Part I. Pol Arch Med Wewn 125: 73-81, 2015.
50. Dzeshka MS, Brown RA and Lip GY: Patients with atrial fibrillation undergoing percutaneous coronary intervention: Current concepts and concerns: Part II. Pol Arch Med Wewn 125: 172-180, 2015.
51. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Køber L, Torp-Pedersen C, *et al*: Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol 62: 981-989, 2013.
52. Thompson PL and Verheugt FW: Managing antithrombotic therapy in patients with both atrial fibrillation and coronary heart disease. Clin Ther 36: 1176-1181, 2014.
53. Gao F, Zhou YJ, Wang ZJ, Yang SW, Nie B, Liu XL, Jia A and Yan ZX: Meta-analysis of the combination of warfarin and dual antiplatelet therapy after coronary stenting in patients with indications for chronic oral anticoagulation. Int J Cardiol 148: 96-101, 2011.
54. Zhao HJ, Zheng ZT, Wang ZH, Li SH, Zhang Y, Zhong M and Zhang W: 'Triple therapy' rather than 'triple threat': A meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. Chest 139: 260-270, 2011.
55. Saheb KJ, Deng BQ, Hu QS, Xie SL, Geng DF and Nie RQ: Triple antithrombotic therapy versus double antiplatelet therapy after percutaneous coronary intervention with stent implantation in patients requiring chronic oral anticoagulation: A meta-analysis. Chin Med J (Engl) 126: 2536-2542, 2013.
56. Andrade JG, Deyell MW, Khoo C, Lee M, Humphries K and Cairns JA: Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: A systematic review and meta-analysis. Can J Cardiol 29: 204-212, 2013.