

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 CHA₂DS₂-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-bio-medical-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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 2008	0	38	2	49	The primary end point was defined as the occurrence of major bleeding complications (fatal bleeding, a decrease in the blood hemoglobin level $>4\text{g/l}$, 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 <i>et al</i> , 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 <i>et al</i> , 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 <i>et al</i> , 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

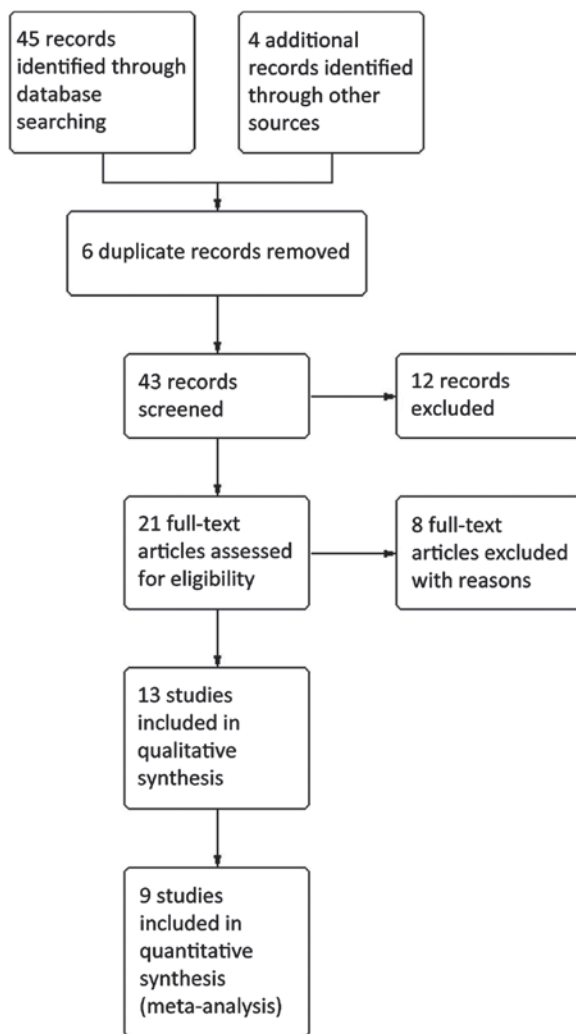


Figure 1. Flow of included studies through the selection process. A total of nine observational trials involving 19,035 patients were included in the meta-analysis.

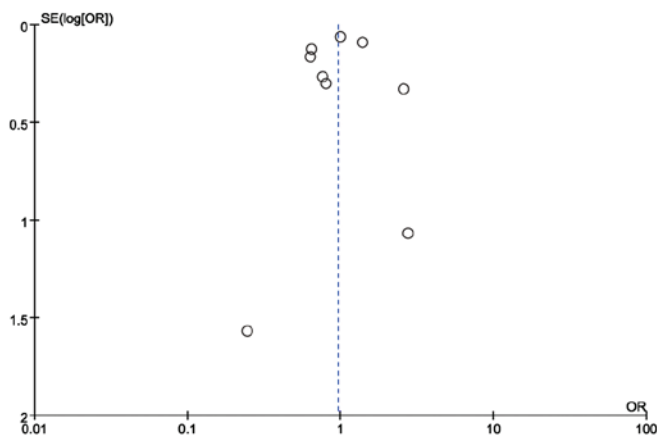


Figure 2. Publication bias assessed by Egger's test. SE, standard error; OR, odds ratio.

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 CHA₂DS₂-VASC score for stroke risk assessment and define 'low-risk' patients as those with a CHA₂DS₂-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,

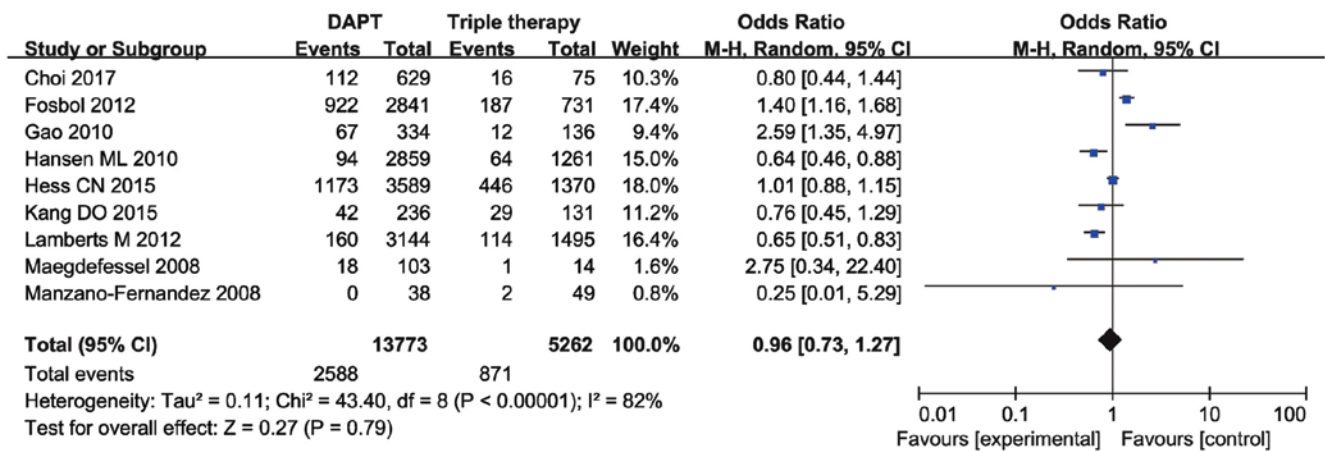


Figure 3. Forest plot showing relative risk of the primary end point incidence. Primary end point incidence was 2,588 patients in the DAPT group ($n=13,773$) and 871 patients in the TOAT group ($n=5,262$) on pooling all nine trials. There was no statistically significant difference in primary end point 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.

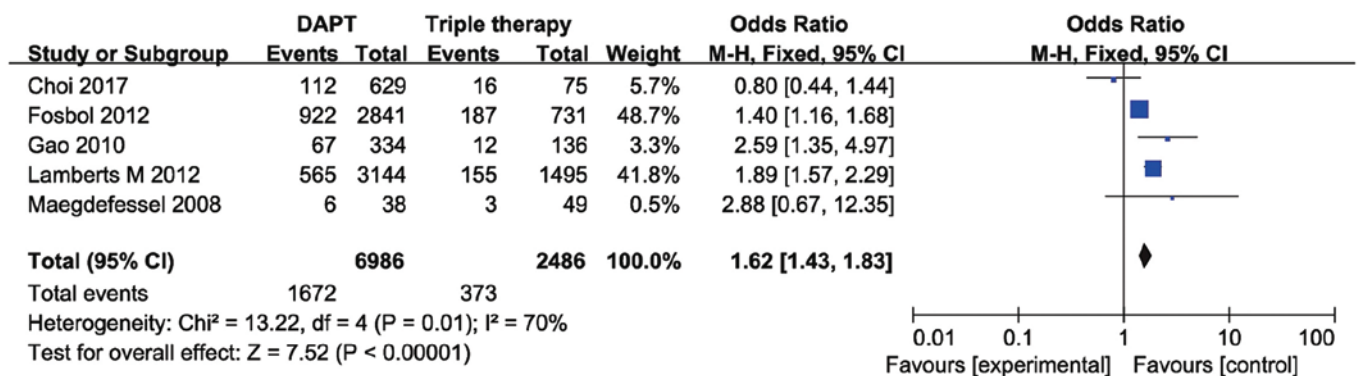


Figure 4. Forest plot showing relative risk of MACE and ischemic stroke. An increased risk of MACE and ischemic stroke was identified in the DAPT group compared with the TOAT group among patients with atrial fibrillation concurrent to percutaneous coronary intervention with stenting ($OR=1.62$, $95\% CI=1.43-1.83$, $P<0.00001$) 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.

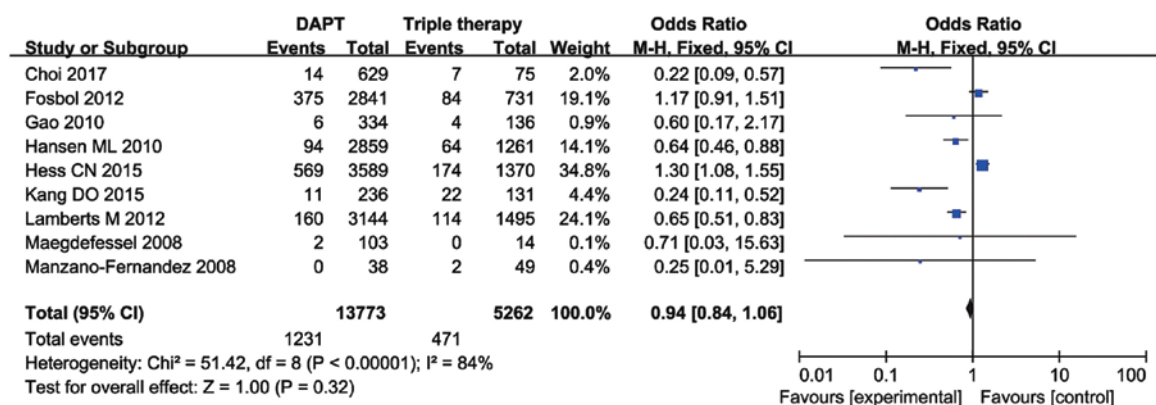


Figure 5. Forest plot showing relative risk of major bleeding events. There was no increased risk of major bleeding in the DAPT group compared with the TOAT group among patients with atrial fibrillation concurrent to percutaneous coronary intervention with stenting ($OR=0.94$, $95\% CI=0.84-1.06$, $P=0.32$). 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).

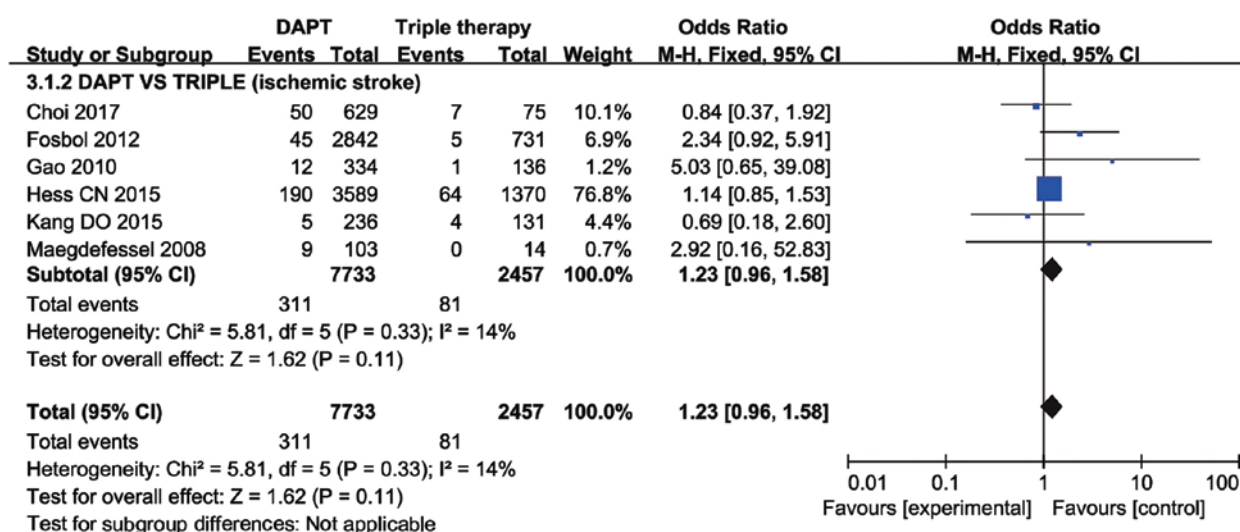


Figure 6. Forest plot showing relative risk of ischemic stroke. There was no increased risk of ischemic stroke in the DAPT group compared with the TOAT group among patients with atrial fibrillation concurrent to percutaneous coronary intervention with stenting ($OR=1.23$, $95\% CI=0.96-1.58$, $P=0.11$) with no significant heterogeneity between the trials ($I^2=14\%$, $P=0.33$). 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 CHADS₂>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.

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