REVIEW

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Triple versus dual oral antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a systematic review and meta-analysis

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Background: The efficacy and safety of dual therapy (dual antiplatelet therapy [DAPT] and warfarin plus single antiplatelet [WS]) versus triple therapy (TT, DAPT plus warfarin) are still debated in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI). The purpose of this study was to determine the optimal antithrombotic strategy. *Methods*: Electronic databases (PubMed, Embase, Cochrane Library, CNKI and WanFang Data) were searched to retrieve studies on the efficacy and safety of TT vs. dual therapy in patients with AF undergoing PCI until August 2017. A meta-analysis was conducted using a random-effects model. The primary efficacy and safety endpoints were major adverse cardiac events (MACEs) and major bleeding events. *Results*: Twenty-four studies involving 21,167 patients were included. The TT group had a significantly lower risk of MACEs (P=0.024) but a higher risk of major bleeding (P<0.001). In TT vs. DAPT subgroup, TT was associated with a lower risk of MI and stent thrombosis in Asian patients and a lower risk of stroke in non-Asian patients. Furthermore, TT did not decrease MACEs incidence (P=0.458) but increased the risk of major bleeding (P=0.008) relative to WS. The same trends were observed in Asian and non-Asian patients. *Conclusion*: Patients with AF undergoing PCI who received TT had significant reduction in MACEs but increased the risk of major bleeding compared with DAPT. However, WS had a similar efficacy but reduced the risk of major bleeding compared with TT. Current evidence suggests that TT might not be required and might be replaced by WS.

1. Introduction

Atrial fibrillation (AF) is the most common clinical arrhythmia, and increases the mortality and stroke risk by 1.5- and 2.5-fold, respectively (Benjamin et al. 1998; Go et al. 2001). Long-term oral anticoagulant (OAC) therapy is the cornerstone that was recommended to prevent ischemic events in patients with AF with a high risk of thrombosis (Cho and Angiolillo 2015; Halvorsen et al. 2017). Up to 30% of these patients with AF have coronary artery disease (CAD) and may be required to undergo percutaneous coronary intervention (PCI) to treat acute coronary syndromes (ACS) (Lip et al. 2014).

Despite direct acting oral anticoagulants (DOACs) appear to be equivalent to warfarin at preventing stroke in patients with atrial fibrillation and to carry a reduced risk of bleeding (Lopez-Lopez et al. 2017), because of the cost of DOACs, their acceptance in developing countries has been low (Pirmohamed 2018). In addition, evidence on DOACs plus antiplatelet in patients with AF undergoing PCI is limited. Therefore, warfarin remains the main choice in patients requiring long-term antithrombotic therapy for AF (Hirsh et al. 2003). Dual antiplatelet therapy (DAPT) usually consists of aspirin and $P2Y_{12}$ receptor inhibitors to reduce recurrent cardiovascular and cerebrovascular events in patients with ACS, especially after undergoing PCI (Levine et al. 2016). However, when AF is combined with PCI, vitamin K antagonist (VKA) cannot effectively prevent stent thrombosis (ST), and DAPT is inferior to VKA in preventing thromboembolism in patients with AF (Lee et al. 2017; Moser et al. 2014; Nikolsky et al. 2012). Currently, the most widely used antithrombotic strategies in the prevention of AF are triple therapy (TT, warfarin, aspirin, and clopidogrel), DAPT, and warfarin plus single antiplatelet (WS) therapy. The optimal anticoagulation strategy is controversial. TT was associated with an increased risk of major bleeding (Andrade et al. 2013; Smith et al. 2012). Moreover, a study of 4959 patients with AF undergoing PCI revealed that TT had higher rates of major bleeding without decreasing major adverse cardiac events (MACEs) rates compared with DAPT (Hess et al. 2015). However, a nationwide cohort study reported that TT was not associated with major bleeding but had a lower incidence of thrombotic events than DAPT (Jin-hua and Ling 2017). An effective method to combine these remains unclear. The European Society of Cardiology (ESC) guidelines recommended that TT (OAC, aspirin, and clopidogrel) or dual therapy (VKA and clopidogrel) should be given in the short term, following which OAC and clopidogrel should be continued up to 12 months in patients with AF undergoing PCI (Lip et al. 2014). The 2012 American College of Chest Physicians (ACCP) guidelines suggested TT from 1 month (bare metal stents [BMS]) to 3–6 months (drug-eluting stents [DES]) followed by VKA plus a single antiplatelet until 12 months (Lansberg et al. 2012). In addition, 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society (ACC/AHA/HRS) guidelines recommended warfarin for patients with ACS and AF (CHA_2DS_2–VASc score ≥2) unless contraindicated (January et al. 2014). However, in clinical practice, the guideline for antithrombotic therapy in patients with AF undergoing PCI is poorly followed. OAC and antiplatelet therapy underuse increased the risk of death and MACEs in these patients (Ancedy et al. 2016). The optimal antithrombotic strategy in patients with AF undergoing PCI is still uncertain.

To assess this issue, multiple meta-analyses were performed (Bavishi et al. 2016; Chen et al. 2015; Saheb et al. 2013). However,

they pooled the unadjusted odds ratio or risk ratio (RR) directly without considering potential confounding factors of studies which may affect the accuracy of the results. Moreover, published meta-analyses compared TT with dual therapy (DAPT or WS) in patients with AF, deep venous thromboembolism, and pulmonary embolism and those who underwent mechanical valve surgery. The major limitation could be the difference in disease characteristics that resulted in heterogeneity. At present, specific meta-analyses on TT vs. DAPT/WS in patients with AF undergoing PCI are limited. In addition, the results of some studies (Amano et al. 2017; Choi et al. 2017; De Vecchis et al. 2016; Feng and Tianchang 2017; Jin-hua and Ling 2017; Rilinger et al. 2016; Sambola et al. 2016b) were published in the past 3 years, parts of which were inconsistent with the previous meta-analyses (Amano et al. 2017; De Vecchis et al. 2016; Jin-hua and Ling 2017). Therefore, we completed a new meta-analysis to evaluate the three antithrombotic strategies in order to investigate the optimal treatment for patients with AF undergoing PCI.

2. Investigations, results and discussion

2.1. Literature search

We identified 1059 potentially eligible articles in our initial electronic search. In total, 85 duplicate articles were eliminated, and 975 irrelevant citations were excluded by reading the abstract. A total of 29 studies were evaluated in detail. Finally, 24 studies (Amano et al. 2017; Choi et al. 2017; Dabrowska et al. 2013; De Vecchis et al. 2016; Fang and Dong-xian 2012; Feng and Tianchang 2017; Fosbol et al. 2013; Gao et al. 2010; Goto et al. 2014; Hess et al. 2015; Ho et al. 2013, Jin-hua and Ling 2017; Kang et al. 2015; Kawai et al. 2015; Lamberts et al. 2012; Maegdefessel et al. 2008; Mennuni et al. 2015; Pilgrim et al. 2013; Rilinger et al. 2016; Rubboli et al. 2014; Ruiz-Nodar et al. 2008; Sambola et al. 2016a, b; Suh et al. 2014) were included in our meta-analysis after excluding 5 studies (2 studies were warfarin alone antithrombotic therapy (Fauchier et al. 2015; Seivani et al. 2013), 2 studies compared patients with AF and those without AF (Bramlage et al. 2013; Lopes et al. 2009), and 1 study compared octogenarian and non-octogenarian patients with AF undergoing PCI (Caballero et al. 2013). A manual search did not find any new eligible studies. The flowchart of study selection is shown in Fig. 1.

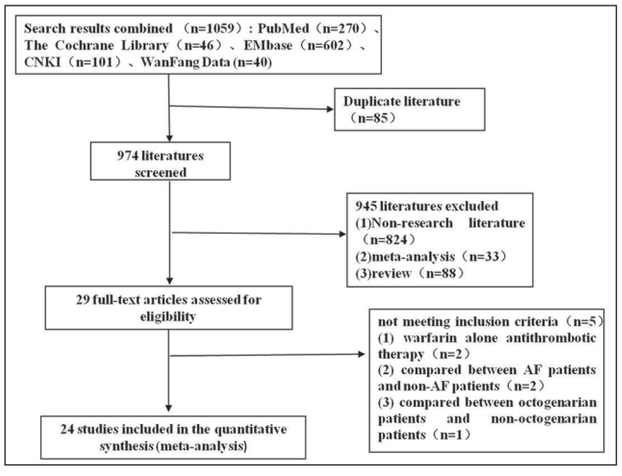

Fig. 1: Flow chart of study selection

2.2. Study characteristics

A total of 21167 patients from 24 studies were included (9144 patients who received TT, 9790 patients who received DAPT, and 2233 patients who received WS). There was no RCT meeting the inclusion criteria, 4 prospective studies were included (Dabrowska et al. 2013; Rubboli et al. 2014; Sambola et al. 2016a, b), and the rest were retrospective studies. Among the included studies, 10 studies were performed in Asia (Amano et al. 2017; Choi et al. 2017; Fang and Dong-xian 2012; Feng and Tianchang 2017; Gao et al. 2010; Goto et al. 2014; Jin-hua and Ling 2017; Kang et al. 2015; Kawai et al. 2015; Suh et al. 2014), 4 in North America (Fosbol et al. 2013; Hess et al. 2015; Ho et al. 2013; Mennuni et al. 2015), and 11 in Europe. The methodological quality of the included studies was assessed using the NOS. Of the included studies, 18 studies were of high quality (NOS ≥7), whereas 6 studies were of low quality (NOS ≤6). The follow-up period of studies was more than 1 month. The main characteristics of the study populations are shown in Table 1, including previous hypertension, stroke, heart failure, stent type, MACEs definition, and methodological quality assessment scores.

2.3. Main analysis for TT (warfarin plus DAPT) versus DAPT

The main analysis included 22 studies (Choi et al. 2017; Dabrowska et al. 2013; De Vecchis et al. 2016; Fang and Dong-xian 2012; Fosbol et al. 2013; Gao et al. 2010; Goto et al. 2014; Hess et al. 2015; Ho et al. 2013; Jin-hua and Ling 2017; Kang et al. 2015; Kawai et al. 2015, Lamberts et al. 2012; Maegdefessel et al. 2008; Mennuni et al. 2015; Pilgrim et al. 2013; Rilinger et al. 2016; Rubboli et al. 2014; Ruiz-Nodar et al. 2008; Sambola et al. 2016a,b; Suh et al. 2014) accounting for 18686 patients with AF undergoing PCI. TT significantly decreased MACEs by 16%, from 25% with DAPT to 21% with TT (pool RR, 0.85; 95% CI, 0.74–0.98; P=0.024; ARR, 4.0%; 95% CI, 3.36%–4.64%; NNT=25); had moderately reduced ST (1.1% vs. 2%; RR, 0.55 [0.31–1.00]; P=0.05; ARR, 0.9% [0.51%–1.29%]; NNT=112); and decreased the risk of MI (RR, 0.76 [0.57–1.01]; P=0.06; ARR, 0.7% [0.18%–1.22%]; NNT=143). Safety analysis showed that TT increased the risk of major bleeding by 35% (12% vs. 7.8%; RR, 1.59 [1.27–1.94]; P<0.001; ARR, 4.2% [3.49%–4.91%]; NNT=24) compared with DAPT. There was no difference regarding the risk of death (P=0.212) and stroke (P=0.403). All results are shown in Table 2.

The potential evidence of heterogeneity was indicated in MACEs (P=0.001) and major bleeding (P=0.001) across the studies. A sensitivity analysis was performed, and the results showed that the conclusion was not affected after excluding each study. The pooled estimate effect size for the study omitted changed from 0.83 (0.72–0.97) to 0.90 (0.82–0.99) in MACEs and from 1.46 (1.18–1.80) to 1.61 (1.30–1.98) in major bleeding. All results were confirmed by the fixed-effects model.

2.4. Meta-regression and subgroup analysis for TT (warfarin plus DAPT) versus DAPT

The meta-regression model showed a linear relationship between the RR of MACEs and publication year (R^2 = 0.94, P<0.001 by meta-regression). We performed the subgroup analysis according to the publication year of MACEs analysis, divided into the earlier subgroup (year ≤2012) (P=0.950 for heterogeneity), mid-year subgroup (2012 > year ≤ 2014) (P= 0.502), and recent subgroup (year >2014) (P= 0.870).

A cumulative meta-analysis of MACEs, which sorts trials chronologically, was performed. The result indicated that TT significantly reduced the incidence of MACEs compared with DAPT until adding a 2013 publication (Dabrowska et al. 2013) (RR, 0.92 [0.80–1.06]). Thereafter, when data from the studies by Suh et al. (2014), Hess et al. (2015), De Vecchis et al. (2016) and Sambola et al. (2016b) were included in the input, the resultant difference was not statistically significant. In contrast, an essential change was observed when data from some other studies (Choi et al. 2017; Jin-hua and Ling 2017; Rilinger et al. 2016) were added (RR, 0.83 [0.77–0.89]).

Moreover, we conducted some subgroup analyses in accordance with risk factors of AF and PCI, including Asian and non-Asian people, age ≥65 years, CHA_2DS_2 score ≥2, and HAS-BLED score ≥3 subgroups. The results of the subgroup analyses are shown in Table 3.

In the publication year subgroup, TT significantly decreased MACEs compared with DAPT in the earlier subgroup (RR,

Table 1: Basic characteristics of the studies

Trial name and year	n	Mean age	Male (%)	DM (%)	Prior MI (%)	Prior Stroke (%)	Prior HF (%)	Follow-up month	Country (%)	Interventions			Stent Type (%)	study Type	Primary end-point	MACEs Defi-nition	Overall Quality
										TT (n)	DAPT (n)	WS (n)					
Asian																	
Gao et al. (2010)	622	71	72	37	18	14	21	12m	China	142	355	125 C	DES(100)	retrospective	①②③④⑤⑥	②③④⑤	8
Suh et al. (2014)	203	66	68	36	4	14	27	42m	Korea	37	166		DES (82)	retrospective	①②③④⑤⑥	②③④⑤	8
Kang et al. (2015)	367	67	64	31	8	NA	23	24m	Korea	131	236		DES (100)	retrospective	①②③⑤⑥	②③⑤	8
Kawai et al. (2014)	146	72	71	45	45	24	NA	12m	Japan	28	67	51 A	DES (78)	retrospective	①②③⑤⑥	②③⑤	8
Goto et al. (2014)	1057	72	73	34	12	19	40	60m	Japan	506	551		DES (48)	retrospective	①②③④⑤⑥	②③⑤	8
Amano (2016)	64	67	72	35	52	17	36	12m	Japan	27		37 A/C	NA	retrospective	①②③④⑤⑥	②③④⑤	7
Choi (2017)	704	68	73	31	10	18	8	12m	Korea	75	629		DES (100)	retrospective	①②③④⑤⑥	②③④⑤	8
Feng and Tianchang (2017)	211	67	73	42	NA	NA	NA	60m	China	141		70 A/C	NA	retrospective	①②⑥	②③④⑤	7
Jin-hua and Ling (2017)	64	66	61	NA	17	NA	NA	12m	China	21	16	27 A	NA	retrospective	①②③⑤⑥	②③⑤	6
Fang and Ding-sian (2012)	180	59	72	36	13	13	20	12m	China	60	120		NA	retrospective	①②③④⑤⑥	②③④⑤	6
Non-Asian																	
Hess et al. (2015)	4959	77	63	32	29	11	19	24m	America	3589	1370		DES (51)	retrospective	①②③⑤	②③	8
De Vecchis et al. (2016)	98	72	46	35	25	13	15	12m	Italy	48	19	31 A/C	NA	retrospective	①②③④⑤⑥	②③④⑤	7
Dabrowska et al. (2013)	104	69	66	28	43	11	NA	1m	Poland	44	60		DES (27)	prospective	①④⑥	②③⑤	6
Sambola et al. (2016b)	289	79	65	35	39	15	27	12m	Spain	159	130		DES (36)	prospective	①②④⑥	②④	7
Lamberts et al. (2012)	6476	71	65	18	51	10	27	12m	Denmark	1495	3144	1837 A/C	NA	retrospective	①②③⑤⑥	②③⑤	7
Sambola (2016a)	585	73	75	38	33	15	56	12m	Spain	319	266		DES (40)	prospective	①⑥	②③④	7
Ruiz-Nodar et al. (2008)	426	72	70	40	44	16	27	20m	Spain	242	184		DES (40)	retrospective	①②③⑤⑥	②③⑤	7
Mennuni et al. (2015)	859	73	75	41	32	12	54	12m	America	371	488		MBS(33)	retrospective	①②③④⑥	②③④	8
Fosbol et al. (2013)	1648	77	60	36	32	15	25	12m	America	448	1200		DES (80)	retrospective	①②③④⑥	②③④	7
Ho et al. (2013)	602	71	67	35	NA	12	49	24m	Canada	382	220		NA	retrospective	①②③⑤⑥	②③⑤	6
Rubboli et al. (2014)	914	73	70	36	25	17	20	12m	European	679	162	73 C	NA	prospective	①②③④⑤⑥	②③④⑤	7
Rilinger et al. (2016)	167	75	71	37	20	NA	NA	1m	Germany	124	43		NA	retrospective	①⑥	②③④	6
Maegdefessel1 et al. (2008)	117	68	75	23	16	13	NA	17m	Germany	14	103		NA	retrospective	①②③⑤⑥	②③⑤	6
Pilgrim et al. (2013)	323	72	73	21	48	11	42	48m	European	62	261		DES (100)	retrospective	①②③⑤⑥	②③⑤	7

Note: DM: diabetes mellitus; MI: myocardial infarction; HF: heart failure; DES: drug eluting stent; MBS: metal bare stent; NA: Not Available; DAPT: dual antiplatelet therapy; TT: dual antiplatelet plus warfarin; WS: Warfarin plus Single antiplatelet; A: aspirin; C: clopidogrel; Primary end-point: ①major adverse cardiac events (MACEs) ②myocardial infarction (MI) ③cardiovascular death ④stroke ⑤stent thrombosis ⑥major bleeding;

Table 2: Results of TT vs. DAPT in patients with AF undergoing PCI

Endpoint	Study n	P (Q test)	Pool RR(95%CI)	P value	ARR (95%CI)	NNT
MACEs	22	0.001	0.85 (0.74 – 0.98)	0.024*	4.0% (3.36%-4.64%)	25
MI	14	0.193	0.76 (0.57 – 1.01)	0.060	0.7% (0.18%-1.22%)	143
Death	16	0.269	0.91 (0.77 – 1.06)	0.212	2.4% (1.64%-3.16%)	42
Stroke	14	0.251	0.88 (0.66 – 1.18)	0.403	1.2% (0.76%-1.96%)	83
ST	9	0.979	0.55 (0.31 – 1.00)	0.05*	0.9% (0.51%-1.29%)	112
Major bleeding	21	0.001	1.57 (1.27 – 1.94)	<0.001*	4.2% (3.49%-4.91%)	24

Note: RR = relative risk; CI = confidence interval; *= statistically significant; ARR = absolute risk reduction; NNT = the number needed to treat

Table 3: Results of TT vs. DAPT in the subgroups

Subgroup	Endpoint	P Q test	Pool RR(95%CI)	P value	ARR(95%CI)	NNT
Asian	MACEs	0.116	0.82(0.65–1.04)	0.094	3.5% (0.5%-6.5%)	29
	MI	0.933	0.46(0.29–0.73)	0.001*	2.6% (1.1%-4.1%)	39
	Death	0.646	0.87(0.70–1.09)	0.223	3.5% (0.7%-6.3%)	29
	Stroke	0.412	1.13(0.84–1.53)	0.403	2.0% (-0.2%-4.2%)	50
	ST	0.870	0.46(0.21–1.00)	0.05*	1.1% (0.2%-2.0%)	91
	Major bleeding	0.000	2.46(1.20-5.04)	0.014*	7.0% (4.7%-9.3%)	15
Non-Asian	MACEs	0.001	0.88(0.65–1.04)	0.189	4.5% (3.2%-5.8%)	23
	MI	0.325	0.94(0.72–1.23)	0.658	0.2% (-0.9%-1.3%)	500
	Death	0.104	0.93(0.72–1.19)	0.547	5.0% (3.2%-6.8%)	20
	Stroke	0.424	0.74(0.53–1.02)	0.068	2.0% (1.1%-2.9%)	50
	ST	0.961	0.72(0.28–1.80)	0.476	0.8% (-0.9%-2.5%)	125
	Major bleeding	0.246	1.44(1.23–1.69)	<0.001*	1.8% (0.1%-3.5%)	56
CHA2DS2≥2	MACEs	0.415	1.05(0.90–1.23)	0.537	3.2% (1.2%-5.2%)	32
Age≥65	MACEs	0.000	0.99(0.61–1.62)	0.970	-	-
HAS-BLED≥3	Major bleeding	0.611	1.79(1.37–2.32)	<0.001*	-	-
year≤2012	MACEs	0.950	0.57(0.49–0.66)	<0.001*	-	-
2012<year≤2014	MACEs	0.502	0.88(0.79–0.98)	0.016*	-	-
year>2014	MACEs	0.870	0.99(0.88–1.12)	0.919	-	-

Note: RR = relative risk; CI = confidence interval; ARR = absolute risk reduction; NNT = the number needed to treat; *= statistically significant

0.57 [0.49–0.66]; P<0.001) and mid-year subgroup (RR, 0.88 [0.79–0.98], P=0.016), but no difference in recent subgroup was observed (P=0.919). Furthermore, in the Asian subgroup, TT was associated with a lower risk of MI (RR, 0.46 [0.29–0.73]; P=0.001; ARR, 2.6% [1.10%–4.10%]; NNT=39) and ST (RR, 0.46 [0.21–1.00]; P=0.05; ARR, 1.1% [0.2%–2.0%]; NNT=91) but a significantly higher risk of major bleeding (RR, 2.46 [1.20–5.04]; P=0.014; ARR, 7.0% [4.7%–9.3%]; NNT=15) compared with DAPT. There was no significant difference in MACEs (P=0.094), death (P=0.223), and stroke (P=0.403) between TT and DAPT. However, in the non-Asian subgroup, TT numerically reduced the risk of stroke (P=0.068) but had a greater risk of major bleeding (RR, 1.44 [1.23–1.69]; P<0.001; ARR, 1.8% [0.1%–3.5%]; NNT=56). The pooled RR showed no significant difference in MACEs (P=0.189), MI (P=0.658), death (P=0.547), and ST (P=0.476). Moreover, TT did not improve the incidence of MACEs in the age ≥65 years subgroup (P=0.970) and higher-risk thrombosis (CHA_2DS_2 score ≥2) subgroup (P=0.537), but increased the incidence of major bleeding in the higher-risk bleeding (HAS-BLED score ≥3) subgroup (RR, 1.79 [1.37–2.32]; P<0.001) relative to DAPT.

Heterogeneity was observed in the magnitude of effect (MACEs, P=0.001 for the non-Asian subgroup and P=0.000 for age ≥65 years subgroup, and major bleeding, P=0.000 for the Asian subgroup). According to the meta-influence analysis, we sequentially excluded the individual study from each subgroup, the results were not affected. The pooled estimate effect size changed from 0.85 (0.69–1.04) to 0.97 (0.87–1.08) for MACEs in the non-Asian subgroup, from 0.82 (0.54–1.25) to 1.12 (0.72–1.73) for MACEs in the age ≥65 years subgroup, and from 2.11 (1.01–4.41) to 3.03 (1.22–7.51) for major bleeding in the Asian subgroup. All results were confirmed by the fixed-effects model.

2.5. TT versus WS in patients with AF undergoing PCI

The main analysis included 8 studies (Amano et al. 2017; De Vecchis et al. 2016; Feng and Tianchang 2017; Gao et al. 2010; Jin-hua and Ling 2017; Kawai et al. 2015; Lamberts et al. 2012; Rubboli et al. 2014) accounting for 4822 patients with AF undergoing PCI, of which 2575 patients received TT and 2247 patients treated with WS. The pooled RR showed no significant difference in ischemic endpoint, including MACEs (P=0.458), MI (P=0.679), death (P=0.313), stroke (P=0.976), and ST (P=0.683) but an increased risk of major bleeding (RR, 1.55 [1.12–2.13]; P=0.008; ARR, 4.8% [3.63%–5.97%]; NNT=21). Moreover, TT did not improve the incidence of ischemic events in both Asian (MACEs, P=0.68; MI, P=0.484; death, P=0.647; stroke, P=0.847; and ST, P=0.772) and non-Asian (MACEs, P=0.372; MI, P=0.725; death, P=0.171; stroke, P=0.575; and ST, P=0.489) subgroups compared with WS but had significantly increased the risk of major bleeding in the non-Asian subgroup (P=0.004; ARR, 4.6% [3.24%–5.96%]; NNT=22). The results are shown in Fig. 2 and Table 4.

Table 4: Results of TT vs. WS in patients with AF undergoing PCI

Group	Endpoint	P Q test	Pool RR(95%CI)	P value	ARR(95%CI)	NNT
Main	MACEs	0.062	1.13(0.82– 1.55)	0.458	0.9% (-0.1%-1.90%)	112
	MI	0.522	0.88(0.47- 1.64)	0.679	1.3% (0.27%-2.33%)	77
	Death	0.193	1.35(0.75 -2.43)	0.313	4.3% (3.11%-5.49%)	24
	Stroke	0.968	1.01(0.52– 1.97)	0.976	0.2% (-0.62%-0.82%)	500
	ST	0.400	0.80(0.27 -2.38)	0.683	0.07% (-0.79%-0.93%)	1429
	Major bleeding	0.368	1.55(1.12- 2.13)	0.008*	4.8% (3.63%-5.97%)	21
Asian	MACEs	0.026	1.21(0.65–1.94)	0.680	1.2% (-1.97%-4.37%)	84
	MI	0.332	0.71(0.27–1.86)	0.484	1.4% (-0.60%-3.40%)	72
	Death	0.123	1.20(0.55–2.64)	0.647	2.1% (-0.26%-4.46%)	48
	Stroke	0.904	0.93(0.15–1.92)	0.847	1.2% (-0.91%-3.31%)	84
	ST	0.162	1.48(0.10–21.3)	0.772	0.5% (-0.88%-1.88%)	200
	Major bleeding	0.196	2.63(0.93–7.44)	0.069	6.6% (4.03%-9.17%)	16
Non-Asian	MACEs	0.313	1.16(0.84-1.60)	0.372	1.2% (0.16%-2.24%)	84
	MI	0.935	1.18(0.47-2.94)	0.725	2.2% (0.93%-3.37%)	46
	Death	0.400	1.80(0.78-4.15)	0.171	6.6% (5.34%-7.86%)	16
	Stroke	0.892	1.63(0.30–8.94)	0.575	1.3% (0.61%-1.99%)	77
	ST	0.433	0.62(0.16-2.40)	0.489	0.5% (-0.91%-1.91%)	200
	Major bleeding	0.989	1.41(1.11-1.79)	0.004*	4.6% (3.24%-5.96%)	22

Note: RR = relative risk; CI = confidence interval; ARR = absolute risk reduction; NNT = the number needed to treat; *= statistically significant

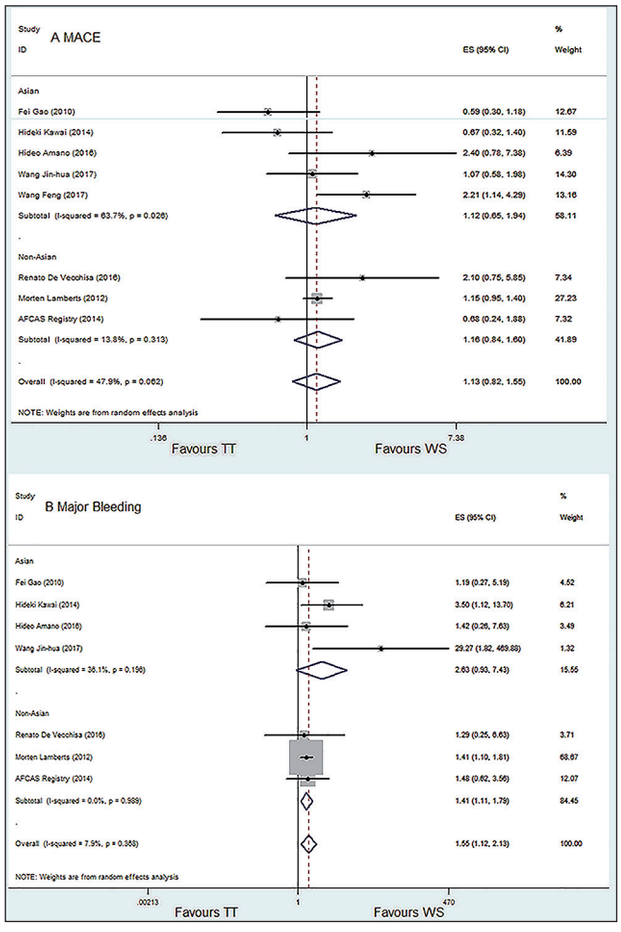

Fig. 2: TT compared with WS in AF patients undergoing PCI: (A) MACE; (B) Major Bleeding

No significant heterogeneity was observed in evaluated endpoints (P>0.05). When we sequentially omitted each study from the analysis, the results were not affected. All results were confirmed by the fixed-effects model.

2.6. Publication bias

Visual inspection of the funnel plots did not show any evidence of obvious asymmetry for MACEs and major bleeding in the TT vs. WS group and for MACEs in the TT vs. DAPT group. Egger's and Begg's tests revealed no significant publication bias for study outcomes (TT vs. WS, MACEs, Egger's test P=0.964, Begg's test P=0.902; major bleeding, Egger's test P=0.213, Begg's test P=0.230; TT vs. DAPT, MACEs, Egger's test P=0.961, Begg's test P=0.102). However, Egger's test showed potential publication bias for major bleeding (Egger's test, 0.049) in the TT vs. DAPT group. The result was not affected after adding eight possible missing studies using the trim and fill method.

2.7. Conclusion

Patients with AF undergoing PCI who received TT showed a significant reduction in the risk of MACEs but an increased risk of major bleeding compared with those who received DAPT. However, compared with TT, the WS therapy, which had a similar efficacy but reduced the risk of major bleeding, might be more appropriate for these patients. Current evidence suggests that warfarin plus DAPT might not be required and might be replaced by warfarin plus single antiplatelet.

3. Discussion

Our systematic review and meta-analysis including 21167 patients in 24 observational studies explored the optimal anticoagulant strategy in patients with AF undergoing PCI. The comprehensive results indicated that TT significantly reduced the incidence of MACEs, ST, and MI compared with DAPT. However, TT clearly increased the risk of major bleeding specially for patients with a HAS-BLED score ≥3. Moreover, our subgroup analysis demonstrated that TT significantly reduced the risk of MACEs, ST, and MI in Asian patients and the risk of stroke in non-Asian patients. In addition, whether in the Asian or non-Asian subgroup or main analysis, TT did not decrease the incidence of thrombotic complications and mortality but increased the risk of bleeding in patients

with AF undergoing PCI compared with WS therapy. WS might be a better anticoagulation strategy because it had a similar antithrombotic effect and reduced the risk of major bleeding.

To date, the recommendations of the guidelines for TT are based on some observational studies rather than large RCTs. Therefore, the optimal antithrombotic regimen is uncertain in patients with AF undergoing PCI. The "What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing" (WOEST) study, which is the first open-label, multicenter RCT to evaluate antithrombotic strategy, enrolled 573 patients with stent implantation requiring anticoagulation therapy within 12 months of follow-up. The study indicated that treatment with warfarin and clopidogrel was associated with a significantly lower risk of bleeding complications than TT (warfarin, aspirin, and clopidogrel) without increasing the risk of thrombotic events (Dewilde et al. 2013). Although the WOEST study included only 69% of patients with AF undergoing PCI, the overall results were consistent with our meta-analysis. The "Antithrombotic Strategy Variability In ATrial Fibrillation and Obstructive Coronary Disease Revascularized with PCI" (AVIATOR 2) observational registry enrolled 2500 patients with non-valvular AF undergoing PCI and compared the safety and efficacy of an antithrombotic regimen including WS versus DAPT alone or TT (Chandrasekhar et al. 2015). The study is ongoing and will provide new insights for the physician to manage the anticoagulant therapy. Currently, there is an urgent need for high-quality controlled clinical trials to determine the optimal antithrombotic therapy for these patients. A large number of patients need optimized treatment. Therefore, when we focus on preventing ischemic events, care should be taken for reducing the risk of bleeding.

At present, several studies have been published evaluating the efficacy and safety of antithrombotic therapy to investigate the optimal regimens. Four previous meta-analyses compared TT and DAPT in patients undergoing PCI requiring chronic OAC (Chen et al. 2015; Deshmukh et al. 2013; Grant 2014; Saheb et al. 2013). Their limitation was combining patients with different diseases which have different antithrombotic characteristics, which resulted in heterogeneity. Moreover, one article which compared TT and DAPT in patients with AF undergoing PCI combined the unadjusted odds ratio directly without considering potential confounding factors (Chaudhary et al. 2016). In addition, the specific meta-analysis on TT vs. WS in patients with AF undergoing PCI is limited. Our study combined the adjusted effect estimates to reduce the effect of potential confounding factors. We then strictly limited the type of disease to include all studies involving patients with AF undergoing PCI. Finally, we performed a subgroup analysis for Asian and non-Asian patients considering the influence of race on disease and efficacy of warfarin to evaluate the antithrombotic regimens.

Considering the influence of race/ethnicity on anticoagulation and AF, we performed subgroup analyses by examining Asian and non-Asian populations separately. The results showed that TT significantly reduced the risk of MI and ST in Asian patients and slightly decreased the incidence of stroke in non-Asian patients but increased the risk of major bleeding in Asian and non-Asian patients compared with DAPT. Although anticoagulant therapy had been shown to prevent AF-related thrombotic events, the evidence in the Asian population was limited (Ma 2012). The prevalence of cerebrovascular disease (CVD) in Asian populations may be different from those in European and American populations (Goto et al. 2011). A study reported that warfarin-related intracranial hemorrhage (ICH) in Asian patients were significantly higher than in Caucasian patients (Shen et al. 2007). In addition, Asian patients might be more sensitive to warfarin, because Asian patients with AF required a lower dose to maintain the target international normalized ratio (INR) than non-Asian patients (Rieder et al. 2005). Several factors may have contributed to the failure of warfarin to significantly reduce the risk of stroke in Asian patients, including a rich diet culture, experience of adjusting warfarin doses, inadequate education of patients, and ethnic gene (Limdi and Veenstra 2008). When comparing TT with WS, no significant differences in ischemic events were observed between the Asian and non-Asian subgroups, including MACEs, MI, ST, death, and stroke. However, TT posed a higher risk of major bleeding for non-Asian than Asian patients. This may be related to the range of warfarin-adjusted INR across Asian and non-Asian populations. In elderly patients with AF, the target range of INR should be maintained at 1.8–2.5 based on the Chinese guidelines (Zhang et al. 2015) and 1.6–2.6 based on the Japanese guidelines (2014). Therefore, the risk of major bleeding may be lower in Asian patients.

Of note, from 2013 to 2016, a temporal trend in the effect size (RR) was observed between TT and DAPT in the cumulative meta-analysis for MACE. Possible reasons for this result are as follows. First, the recommended duration of TT varies across different sets of guidelines. The 2012 ACCP guidelines suggested that the duration of TT ranges from 1 month (BMS) to 3–6 months (DES) depending on the stent type (Guyatt et al. 2012). The 2013 ACC/AHA/HRS Task Force Recommendations suggested that TT should be given for 1 month (BMS), 3 months, (sirolimus-eluting stent), and 6 months (paclitaxel-eluting stent) (Anderson et al. 2013). However, the 2014 ESC guidelines for patients with AF at a high risk of stroke (e.g., $CHADS_2$ score ≥2) undergoing PCI recommended that TT should be prolonged to 6 months irrespective of the stent type implanted (Lip et al. 2014). Second, the range of target INR was different. The 2012 ACCP and 2013 ACC/AHA guidelines recommended a target INR of 2.5 (range, 2.0–3.0) during combination of VKA and antiplatelet therapy, whereas the ESC guidelines reduced the target INR to 2.0–2.5. Moreover, in older patients (age ≥75 years), a lower target INR was recommended (range, 1.6–2.5 for ACC/AHA guidelines; 1.8–2.5 in China (Zhang et al. 2015); 1.6–2.6 in Japan (2014)). Therefore, the differences in practice might result in the effect size shift.

The limitations of our meta-analysis should be considered. The main limitation was that our study included several retrospective observational studies which inevitably introduced selection bias and confounding bias. Second, $CHADS_2$ scores for the included studies were inconsistent. Although a subgroup analysis of high thrombotic risk was performed, some studies did not report the stratification of thrombotic risk. Moreover, the range of target INR was not uniform among the studies, of which it is 1.6–2.6 (Amano et al. 2017; Fang and Dong-xian 2012; Gao et al. 2010; Goto et al. 2014; Jin-hua and Ling 2017) in the Asian controls and 2.0–3.0 in other patients (Choi et al. 2017; Kang et al. 2015; Rubboli et al. 2014). The difference in antithrombotic intensity will affect the endpoint outcomes. In addition, the time in therapeutic range (TTR) was related to the risk of thromboembolism and bleeding with VKA (De Caterina et al. 2013; Senoo and Lip 2016). The Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) study had shown that a higher TTR was associated with better bleeding outcomes during follow-up in patients with AF undergoing PCI receiving TT (Proietti et al. 2017). Finally, the duration of TT was different between studies. Although the ISAR-TRIPLE trial indicated that short-term TT (6 weeks) did not substantially reduce the risk of bleeding (Fiedler et al. 2015), an extended duration of TT (>6 months) might have the potential to cause considerable harm in patients with AF undergoing PCI (Piccini and Jones 2017).

4. Experimental

4.1. Data sources, search strategy, and selection criteria

We conducted and reported this systematic review and meta-analysis in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group (Stroup et al. 2000) and the Cochrane Handbook (Cochrane 2011). To identify all eligible studies of TT vs. dual therapy in patients with AF undergoing PCI, we performed a systematic search, without language restrictions, on PubMed, Embase, Cochrane Library, WanFang Data, and CNKI databases from January 1980 to August 2017. The following keywords were used: ("Dual therapy" OR "Anticoagulation" OR "warfarin" OR "Dual antiplatelet therapy" OR "DAPT") AND ("Anticoagulation" OR "warfarin" OR "Triple therapy") AND ("Atrial fibrillation" OR "AF") AND ("percutaneous coronary intervention" OR "PCI" OR "stents") as search terms (Figure S1 for the search strategy). We also performed a manual search of the reference lists of studies, reviews, and pertinent meta-analyses on this topic.

The literature search was independently undertaken by two authors (Y.D. and Y.W.) using a standardized approach. Any disagreements between the two authors were settled by the primary author (R.L.M) until a consensus was reached. The studies were included following the inclusion criteria: (1) the studies were case-control or cohort

studies or randomized controlled trials (RCTs); (2) the studies compared TT (DAPT plus warfarin) with dual therapy (DAPT or WS); (3) the risk estimates and 95% confidence intervals (CIs) were reported, and the ischemic and/or bleeding outcomes required to calculate them were available; (4) the patients with AF undergoing PCI were enrolled in the studies; (5) the study included outcomes measured in a follow-up period of ≥1 month. The primary efficacy endpoint was MACEs rate, which used the definitions of the studies concerned (Table 1). The primary safety endpoint was the rate of major bleeding (defined according to the studies concerned). The studies that met the following criteria were excluded: (1) repeated publication; (2) incomplete original data or relevant data cannot be obtained by contacting authors; and (3) basic science studies, review, or case reports.

4.2. Data extraction and quality assessment

Independent data selection, extraction, and evaluation by the two researchers (Y.D. and Y.W.) were designed in accordance with the inclusion and exclusion criteria. The following details were recorded from each study: the first author, publication year, study design, country, number, and mean age. Clinical characteristics including clinical outcomes, diabetes, previous MI (as defined by the American College of Cardiology/American Heart Association definitions), previous stroke, length of follow-up, and stent type were also extracted (Table 1). The methodological quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (Wells et al. 2012).

4.3. Statistical analysis

We first conducted a global meta-analysis for TT vs. DAPT and TT vs. WS in patients with AF undergoing PCI, separately. Some subgroup meta-analyses for TT vs. DAPT were performed, involving Asian and non-Asian, CHA_2DS_2-VASc ≥2, HAS-BLED ≥3, and age ≥65 year subgroups. In the presence of heterogeneity, we used a random-effects model because its assumptions account for the presence of variability among studies. Heterogeneity among studies was investigated using the Q test and I^2 statistic (Demets 1987); a P-value of <0.05 for the Q test was considered indicative of significant heterogeneity (DerSimonian and Laird 1986). The adjusted effect estimates (odds ratios, RRs, and hazard risks [HR]) between TT and dual therapy were extracted. The reported event frequencies were used to calculate RRs with 95% CI in each study. Because the endpoint outcomes were relatively uncommon and the odds ratios in the case-control studies were close to 1, odds ratios were considered approximations of RR (Grant 2014). We calculate the absolute risk reduction (ARR), 95% CI, and number needed to treat (NNT) of the endpoint events. We also performed a sensitivity analysis by removing each individual study from the meta-analysis and used qualitative Egger's (Egger et al. 1997) or Begg's (Begg and Mazumdar 1994) test to check for potential publication bias. All reported P-values are two sided, and a P-value <0.05 was considered statistically significant. Statistical analysis was performed using STATA 12.0 software (StataCorp LP, College Station, TX).

Authors' contributions: Z.C. Cao, X.H. Ren and X.L. Liu designed the study protocol and wrote the manuscript. Y. Dong, Y, Wang and R.L. Ma screened the studies, extracted the data and analysed the data. J.J. Sun critically revised the manuscript. All authors revised critically the work providing substantial input and gave final approval of the version to be published.

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References

Amano H, Saito D, Yabe T, Okubo R, Toda M, Ikeda T (2017) Efficacy and safety of triple therapy and dual therapy with direct oral anticoagulants compared to warfarin. Int Heart J 58: 570-576.

Ancedy Y, Lecoq C, Saint Etienne C, Ivanes F, Angoulvant D, Babuty D, Lip G Y, Fauchier L (2016) Antithrombotic management in patients with atrial fibrillation undergoing coronary stent implantation: What is the impact of guideline adherence? Int J Cardiol 203: 987-994.

Anderson J L, Halperin J L, Albert N M, Bozkurt B, Brindis R G, Curtis L H, DeMets D, Guyton R A, Hochman J S, Kovacs R J, Ohman E M, Pressler S J, Sellke FW, Shen WK (2013) Management of patients with atrial fibrillation (Compilation of 2006 ACCF/AHA/ESC and 2011 ACCF/AHA/HRS Recommendations): A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 127: 1916-1926.

Andrade J G, Deyell M W, Khoo C, Lee M, Humphries K, Cairns JA (2013) Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. Can J Cardiol 29: 204-212.

Bavishi C, Koulova A, Bangalore S, Sawant A, Chatterjee S, Ather S, Valencia J, Sarafoff N, Rubboli A, Airaksinen JK, Lip GYH, Tamis-Holland JE (2016) Evaluation of the efficacy and safety of dual antiplatelet therapy with or without warfarin in patients with a clinical indication for DAPT and chronic anticoagulation: A meta-analysis of observational studies. Catheterization and Cardiovasc Interv 88: E12-E22.

Begg C B, Mazumdar M (1994) Operating characteristics of a rank correlation test for publication bias. Biometrics 50: 1088-1101.

Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D (1998) Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98: 946-952.

Bramlage P, Cuneo A, Zeymer U, Hochadel M, Richardt G, Silber S, Senges J, Nienaber CA, Tebbe U, Kuck KH (2013) Prognosis of patients with atrial fibrillation undergoing percutaneous coronary intervention receiving drug eluting stents. Clin Res Cardiol 102: 289-297.

Caballero L, Ruiz-Nodar J M, Marin F, Roldan V, Hurtado J A, Valencia J, Manzano-Fernandez S, Sogorb F, Valdes M, Lip GY (2013) Oral anticoagulation improves the prognosis of octogenarian patients with atrial fibrillation undergoing percutaneous coronary intervention and stenting. Age Ageing 42: 70-75.

Chandrasekhar J, Mastoris I, Baber U, Sartori S, Schoos M, Bansilal S, Dangas G, Mehran R (2015) Antithrombotic strategy variability in atrial fibrillation and obstructive coronary disease revascularized with PCI-rationale and study design of the prospective observational multicenter AVIATOR 2 registry. Am Heart J 170: 1234-1242.

Chaudhary N, Bundhun P K, Yan H (2016) Comparing the clinical outcomes in patients with atrial fibrillation receiving dual antiplatelet therapy and patients receiving an addition of an anticoagulant after coronary stent implantation: A systematic review and meta-analysis of observational studies. Medicine (Baltimore) 95: e5581.

Chen CF, Chen B, Zhu J, Xu YZ (2015) Antithrombotic therapy after percutaneous coronary intervention in patients requiring oral anticoagulant treatment. A meta-analysis. Herz 40: 1070-1083.

Cho JR, Angiolillo DJ (2015) Percutaneous coronary intervention and atrial fibrillation: the triple therapy dilemma. J Thromb Thrombolysis 39: 203-208.

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

Cochrane (2011) Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. London, England.

Dabrowska M, Ochala A, Cybulski W, Tendera M (2013) Balancing between bleeding and thromboembolism after percutaneous coronary intervention in patients with atrial fibrillation. Could triple anticoagulant therapy be a solution? Postepy Kardiol Interwencyjnej 9: 234-240.

De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C, Huber K, Jespersen J, Kristensen S D, Lip G Y, Morais J, Rasmussen LH, Siegbahn A, Verheugt FW, Weitz J I (2013) Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis--Task Force on Anticoagulants in Heart Disease. Thromb Haemost 110: 1087-1107.

De Vecchis R, Cantatrione C, Mazzei D (2016) Clinical relevance of anticoagulation and dual antiplatelet therapy to the outcomes of patients with atrial fibrillation and recent percutaneous coronary intervention with stent. J Clin Med Res 8: 153-161.

Demets DL (1987) Methods for combining randomized clinical trials: strengths and limitations. Stat Med 6: 341-350.

DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7: 177-188.

Deshmukh A, Hilleman DE, Del Core M, Nair CK (2013) Antithrombotic regimens in patients with indication for long-term anticoagulation undergoing coronary interventions-systematic analysis, review of literature, and implications on management. Am J Ther 20: 654-663.

Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, Adriaenssens T, Vrolix M, Heestermans AA, Vis MM, Tijsen JG, van 't Hof AW, ten Berg JM (2013) Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 381: 1107-1115.

Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ 315: 629-634.

Fang D, Dong-xian H (2012) Comparison of safety and effect between trigeminy antithrombotic therapy and bigeminy antithrombotic therapy in AF complicated CHD patients undergoing PCI. Chin J Cardiovasc Rehabil Med 21: 412-415.

Fauchier L, Greenlaw N, Ferrari R, Ford I, Fox KM, Tardif JC, Tendera M, Steg PG (2015) Use of anticoagulants and antiplatelet agents in stable outpatients with coronary artery disease and atrial fibrillation. International CLARIFY Registry. PLoS One 10: e0125164.

Feng W, Tianchang L (2017) The cross-section study of anti-coagulation in patients undergone percutaneous coronary intervention combining with atrial fibrillation. Translat Med J 6: 99-102.

Fiedler KA, Maeng M, Mehilli J, Schulz-Schupke S, Byrne RA, Sibbing D, Hoppmann P, Schneider S, Fusaro M, Ott I, Kristensen SD, Ibrahim T, Massberg S, Schunkert H, Laugwitz KL, Kastrati A, Sarafoff N (2015) Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: The ISAR-TRIPLE Trial. J Am Coll Cardiol 65: 1619-1629.

Fosbol EL, Wang TY, Li S, Piccini J, Lopes RD, Mills RM, Klaskala W, Thomas L, Roe M T, Peterson ED (2013) Warfarin use among older atrial fibrillation patients with non-ST-segment elevation myocardial infarction managed with coronary stenting and dual antiplatelet therapy. Am Heart J 166: 864-870.

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

Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE (2001) Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 285: 2370-2375.

Goto K, Nakai K, Shizuta S, Morimoto T, Shiomi H, Natsuaki M, Yahata M, Ota C, Ono K, Makiyama T, Nakagawa Y, Furukawa Y, Kadota K, Takatsu Y, Tamura T, Takizawa A, Inada T, Doi O, Nohara R, Matsuda M, Takeda T, Kato M, Shirotani M, Eizawa H, Ishii K, Lee J D, Takahashi M, Horie M, Miki S, Aoyama T, Suwa S, Hamasaki S, Ogawa H, Mitsudo K, Nobuyoshi M, Kita T, Kimura T (2014) Anticoagulant and antiplatelet therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. Am J Cardiol 114: 70-78.

Goto S, Ikeda Y, Chan JC, Wilson PW, Yeo TC, Liau CS, Abola MT, Salette G, Steg PG, Bhatt DL (2011) Risk-factor profile, drug usage and cardiovascular events within a year in patients with and at high risk of atherothrombosis recruited from

Asia as compared with those recruited from non-Asian regions: a substudy of the REduction of Atherothrombosis for Continued Health (REACH) registry. Heart Asia 3: 93-98.
Grant RL (2014) Converting an odds ratio to a range of plausible relative risks for better communication of research findings. BMJ 348: f7450.
Guidelines (2014) Guidelines for Pharmacotherapy of Atrial Fibrillation (JCS 2013). Circulation J 78: 1997-2021
Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ (2012) Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: 7S-47S.
Halvorsen S, Storey RF, Rocca B, Sibbing D, Ten Berg J, Grove EL, Weiss TW, Collet JP, Andreotti F, Gulba DC, Lip GYH, Husted S, Vilahur G, Morais J, Verheugt FWA, Lanas A, Al-Shahi Salman R, Steg P G, Huber K (2017) 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.
Hess CN, Peterson ED, Peng SA, de Lemos JA, Fosbol EL, Thomas L, Bhatt DL, Saucedo JF, Wang TY (2015) Use and outcomes of triple therapy among older patients with acute myocardial infarction and atrial fibrillation. J Am Coll Cardiol 66: 616-627.
Hirsh J, Fuster V, Ansell J, Halperin JL (2003) American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation 107: 1692-1711.
Ho KW, Ivanov J, Freixa X, Overgaard CB, Osten MD, Ing D, Horlick E, Mackie K, Seidelin PH, Dzavik V (2013) Antithrombotic therapy after coronary stenting in patients with nonvalvular atrial fibrillation. Can J Cardiol 29: 213-218.
January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW (2014) 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 130: 2071-2104.
Jin-hua W, Ling L (2017) The efficacy and safety of anticoagulant therapy on atrial fibrillation patients after PCI. J Pract Electrocardiol 26: 125-128.
Kang DO, Yu CW, Kim HD, Cho JY, Joo HJ, Choi RK, Park JS, Lee HJ, Kim JS, Park JH, Hong SJ, Lim DS (2015) Triple antithrombotic therapy versus dual antiplatelet therapy in patients with atrial fibrillation undergoing drug-eluting stent implantation. Coron Artery Dis 26: 372-380.
Kawai H, Watanabe E, Yamamoto M, Harigaya H, Sano K, Takatsu H, Muramatsu T, Naruse H, Sobue Y, Motoyama S, Sarai M, Takahashi H, Arakawa T, Kan S, Sugiura A, Murohara T, Ozaki Y (2015) Major bleeding complications related to combined antithrombotic therapy in atrial fibrillation patients 12 months after coronary artery stenting. J Cardiol 65: 197-202.
Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen S L, Kober L, Torp-Pedersen C, Gislason GH, Hansen ML (2012) 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.
Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA (2012) Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: e601S-e636S.
Lee CJ, Pallisgaard JL, Olesen JB, Carlson N, Lamberts M, Gislason GH, Torp-Pedersen C, Brandes A, Husted SE, Johnsen SP, Hansen ML (2017) Antithrombotic therapy and first myocardial infarction in patients with atrial fibrillation. J Am Coll Cardiol 69: 2901-2909.
Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. (2016) 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 68: 1082-1115.
Limdi NA, Veenstra DL (2008) Warfarin pharmacogenetics. Pharmacotherapy 28: 1084-1097.
Lip GY, Windecker S, Huber K, Kirchhof P, Marin F, Ten Berg JM, Haeusler KG, Boriani G, Capodanno D, Gilard M, Zeymer U, Lane D, Storey RF, Bueno H, Collet JP, Fauchier L, Halvorsen S, Lettino M, Morais J, Mueller C, Potpara TS, Rasmussen LH, Rubboli A, Tamargo J, Valgimigli M, Zamorano JL (2014) 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.
Lopes RD, Elliott LE, White HD, Hochman JS, Van de Werf F, Ardissino D, Nielsen TT, Weaver WD, Widimsky P, Armstrong P W, Granger CB (2009) Antithrombotic therapy and outcomes of patients with atrial fibrillation following primary percutaneous coronary intervention: results from the APEX-AMI trial. Eur Heart J 30: 2019-2028.
Lopez-Lopez JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, Davies PA, Bodalia PN, Bryden PA, Welton NJ, Hollingworth W, Caldwell DM, Savovic J, Dias S, Salisbury C, Eaton D, Stephens-Boal A, Sofat R (2017) Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ 359: j5058.
Ma C (2012) Current antithrombotic treatment in East Asia: some perspectives on anticoagulation and antiplatelet therapy. Thromb Haemost 107: 1014-1018.
Maegdefessel L, Schlitt A, Faerber J, Bond S P, Messow C M, Buerke M, Raaz U, Werdan K, Muenzel T, Weiss C (2008) Anticoagulant and/or antiplatelet treatment in patients with atrial fibrillation after percutaneous coronary intervention. A single-center experience. Med Klin 103: 628-632.
Mennuni MG, Halperin JL, Bansilal S, Schoos MM, Theodoropoulos KN, Meelu OA, Sartori S, Giacoppo D, Bernelli C, Moreno PR, Krishnan P, Baber U, Lucarelli C, Dangas GD, Sharma SK, Kini AS, Tamburino C, Chieffo A, Colombo A, Presbitero P, Mehran R (2015) Balancing the risk of bleeding and stroke in patients with atrial fibrillation after percutaneous coronary intervention (from the AVIATOR Registry). Am J Cardiol 116: 37-42.
Moser M, Olivier CB, Bode C (2014) Triple antithrombotic therapy in cardiac patients: more questions than answers. Eur Heart J 35: 216-223.
Nikolsky E, Mehran R, Dangas GD, Yu J, Parise H, Xu K, Pocock S J, Stone GW (2012) Outcomes of patients treated with triple antithrombotic therapy after primary percutaneous coronary intervention for ST-elevation myocardial infarction (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial). Am J Cardiol 109: 831-838.
Piccini JP, Jones WS (2017) Triple therapy for atrial fibrillation after PCI. N Engl J Med 377: 1580-1582.
Pilgrim T, Kalesan B, Zanchin T, Pulver C, Jung S, Mattle H, Carrel T, Moschovitis A, Stortecky S, Wenaweser P, Stefanini GG, Raber L, Meier B, Juni P, Windecker S (2013) Impact of atrial fibrillation on clinical outcomes among patients with coronary artery disease undergoing revascularisation with drug-eluting stents. EuroIntervention 8: 1061-1071.
Pirmohamed M (2018) Warfarin: the end or the end of one size fits all therapy? J Pers Med 8: pii: E22.
Proietti M, Airaksinen KEJ, Rubboli A, Schlitt A, Kiviniemi T, Karjalainen PP, Lip GY (2017) Time in therapeutic range and major adverse outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: The Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) registry. Am Heart J 190: 86-93.
Rieder MJ, Reiner AP, Gage BF, Nickerson DA, Eby CS, McLeod HL, Blough DK, Thummel KE, Veenstra DL, Rettie AE (2005) Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 352: 2285-2293.
Rilinger J, Meyer M, Schnabel K, Weik P, Charlet A, Esser J S, Zhou Q, Bode C, Moser M, Diehl P, Olivier CB (2016) High platelet reactivity after P2Y12-inhibition in patients with atrial fibrillation and coronary stenting. J Thromb Thrombol 42: 558-565.
Rubboli A, Schlitt A, Kiviniemi T, Biancari F, Karjalainen PP, Valencia J, Laine M, Kirchhof P, Niemela M, Vikman S, Lip GY, Airaksinen KE (2014) One-year outcome of patients with atrial fibrillation undergoing coronary artery stenting: an analysis of the AFCAS registry. Clin Cardiol 37: 357-364.
Ruiz-Nodar JM, Marin F, Hurtado JA, Valencia J, Pinar E, Pineda J, Gimeno JR, Sogorb F, Valdes M, Lip GY (2008) 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 51: 818-825.
Saheb KJ, Deng BQ, Hu QS, Xie SL, Geng DF, Nie RQ (2013) 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.
Sambola A, Mutuberria M, Garcia Del Blanco B, Alonso A, Barrabes J A, Alfonso F, Bueno H, Cequier A, Zueco J, Rodriguez-Leor O, Bosch E, Tornos P, Garcia-Dorado D (2016a) Effects of triple therapy in patients with non-valvular atrial fibrillation undergoing percutaneous coronary intervention regarding thromboembolic risk stratification. Circ J 80: 354-362.
Sambola A, Mutuberria M, Garcia Del Blanco B, Alonso A, Barrabes J A, Bueno H, Alfonso F, Cequier A, Zueco J, Rodriguez-Leor O, Tornos P, Garcia-Dorado D (2016b) Impact of triple therapy in elderly patients with atrial fibrillation undergoing percutaneous coronary intervention. PLoS One 11: e0147245.
Seivani Y, Abdel-Wahab M, Geist V, Richardt G, Sulimov DS, El-Mawardy M, Toelg R, Akin I (2013) Long-term safety and efficacy of dual therapy with oral anticoagulation and clopidogrel in patients with atrial fibrillation treated with drug-eluting stents. Clin Res Cardiol 102: 799-806.
Senoo K, Lip GY (2016) Female sex, time in therapeutic range, and clinical outcomes in atrial fibrillation patients taking warfarin. Stroke 47: 1665-1668.
Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W (2007) Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. J Am Coll Cardiol 50: 309-315.
Smith JG, Wieloch M, Koul S, Braun O, Lumsden J, Rydell E, Öhman J, Scherstén F, Svensson P J, van der Pals J (2012) Triple antithrombotic therapy following an acute coronary syndrome: prevalence, outcomes and prognostic utility of the HAS-BLED score. EuroIntervention 8: 672-678.
Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 283: 2008-2012.
Suh SY, Kang WC, Oh PC, Choi H, Moon CI, Lee K, Han SH, Ahn T, Choi IS, Shin EK (2014) Efficacy and safety of aspirin, clopidogrel, and warfarin after coronary artery stenting in Korean patients with atrial fibrillation. Heart Vessels 29: 578-583.
Wells G, Shea B, O'Connell D, Robertson J, Peterson Jm Welch V, Losos P, Tugwell P (2012) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Ottawa, Ontario: Department of Epidemiology and Community Medicine. V http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
Zhang S, Yang Y, Huang C, Huang D (2015) Guideline of stroke prevention in Chinese patients with atrial fibrillation. Chin J Cardiac Arrhyth 19: 162-173.