

REVIEW ARTICLE

Triple Therapy *Versus* Dual Antiplatelet Therapy for Patients with Atrial Fibrillation and Acute Coronary Syndromes: A Systematic Literature Review

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Abstract: Background: Patients with acute coronary syndromes (ACS) and a history of atrial fibrillation (AF) have indications for both dual antiplatelet therapy (DAPT) and oral anticoagulation (OAC). Triple therapy (TT), the combination of DAPT and OAC, is recommended in guidelines. We examined studies comparing clinical outcomes on DAPT *versus* TT for patients with AF and ACS.

Methods: We searched Medline, Medline pending, EMBASE and Evidence-Based Medicine Reviews databases for studies published between January 2000 to December 2016 in AF patients with ACS that compared DAPT and TT that reported ischaemic and/or bleeding outcomes. Studies that were not purely an AF population were excluded.

Results: Ten studies were included in the review, all of which were observational, 8 of which were retrospective. None of the studies detailed the specifics of treatment allocation. All but one were of AF patients with a mix of stable coronary disease and ACS patients. TT was associated with increased bleeding when compared to DAPT, with adjusted odds ratios ranging from 1.25 to 6.84. While the largest study reported a reduction in stroke associated with TT (odds ratio 0.67), two other studies reported non-significant increases in stroke with TT. Variable composite ischaemic endpoints were reported, none showing a statistical significant difference between DAPT and TT.

Conclusion: In patients with ACS and AF, TT is likely to be associated with increased risk of bleeding, without a clear reduction in ischaemic endpoints. The quality of the evidence to support current guidelines for this patient group was generally poor.

Keywords: Atrial fibrillation, acute coronary syndrome, triple therapy, dual antiplatelet therapy, systematic literature review.

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1. INTRODUCTION

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia and is associated with substantial risk of thromboembolism and mortality [1]. Treatment with an oral anticoagulant (OAC) is considered standard-of-care in patients with AF at moderate to high risk of thromboembolism and is superior to dual antiplatelet therapy (DAPT) with aspirin and clopidogrel for the prevention of ischaemic stroke and systemic embolization [2].

Presentation with acute coronary syndromes (ACS) and concurrent AF is common with studies reporting between 6 and 21% of patients with ACS have concurrent AF [3]. Patients presenting with both ACS and AF tend to be older, have more comorbidities and worse clinical outcomes [4].

Treatment with DAPT for one year is standard-of-care in those presenting with ACS and treatment with DAPT is superior to oral anticoagulants in those undergoing percutaneous coronary intervention (PCI) [5, 6]. Determining the optimal antithrombotic therapy in this group of patients represents an important clinical dilemma.

Current guidelines and consensus expert reports generally recommend individualizing therapy based on a patient's ischaemic and bleeding risk and frequently recommend treatment with triple therapy (TT), a combination of DAPT and OAC therapy, in those with ACS and AF [4, 7, 8]. However the optimal therapy for AF patients with ACS, and the risks and benefits of TT compared with DAPT in this setting have not been established. The original intent of this systematic literature review was to limit the scope of papers included to only those with pure AF and ACS populations. However, due to the limited literature this was expanded to include pure AF and either pure ACS or ACS or coronary artery disease undergoing intervention.

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2. METHODS

2.1. Search Strategy

We electronically searched Medline, Medline pending, EMBASE and Evidence-Based Medicine Reviews (EBMR) databases, using the MeSH terms “atrial fibrillation” AND “acute coronary syndromes” (all fields), “anticoagulants” OR “platelet aggregation inhibitors” (all fields), and the key words “OAC”, “NOAC”, “Warfarin”, “Apixaban”, “Rivaroxaban”, “Dabigatran”, “Darexaban”, “triple therapy” “dual antiplatelet therapy”, “Clopidogrel”, “Prasugrel”, Ticagrelor” and “antiplatelet” in all fields. Results were limited to English language and human populations. In addition, the reference lists of pertinent articles were manually screened for eligible articles. We limited the search strategy to results from 1st January 2000 to 31st December 2016.

2.2. Inclusion Criteria

Studies had to meet all of the following criteria: (1) AF patients with an ACS or coronary artery disease undergoing intervention; (2) comparison of DAPT and TT; (3) inclusion of either ischaemic and/or bleeding outcomes. Studies that were based on mixed populations on anticoagulant therapy that were not purely an AF population were excluded. Where more than one study reported on the same patient population only the most recent report was included.

2.3. Data Extraction

Abstracts were screened to assess eligibility. The full text article was examined for all potentially eligible studies.

3. RESULTS

The search strategy identified 1888 titles. After the removal of duplicates 1599 abstracts were screened. A final set of 10 papers met the inclusion criteria (see Fig. 1) and details of these are given in Table 1. Where author groups published more than one study from largely the same patient population (Sambola *et al.* [9, 10], Lamberts *et al.* [11, 12] & Fosbol *et al.* [13, 14]) only the most recent study was included in the current review. There was considerable heterogeneity between studies with respect to outcomes, patient numbers in the DAPT and TT arms (range n=67 to n=5486) and follow-up periods (6 months - 42 months). Of the 10 studies, only Sambola *et al.* (2016) [9] and Rubboli *et al.* (2014) [15] were prospective in nature.

The proportion of patients with an ACS ranged from 40% in Suh *et al.* (2014) [16] to 100% in Fosbol *et al.* (2013) [13]. In 6 of the 10 studies the proportion of patients with ACS was higher in the DAPT treatment arm than in the TT arm. Details of paroxysmal, persistent and permanent AF groups could not be determined and in all cases the term AF was used to collectively represent these groups. Allocation to

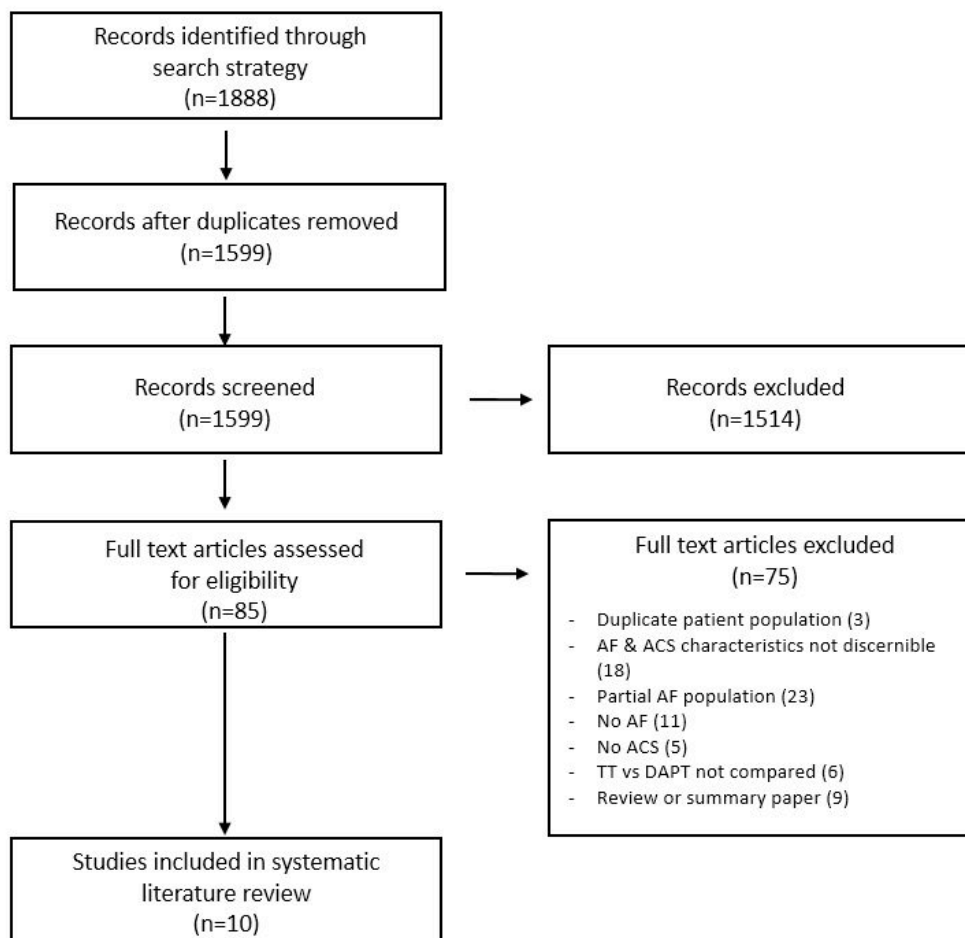


Fig. (1). Flow diagram of study selection.

DAPT or TT was at the discretion of the physician in 6 studies and not described in the remaining 4 studies (Table 1). When treatment was physician determined there were no reports of institutional protocols or schema to assist physician decision making. Nine studies had a follow up duration greater than or equal to 12 months and in these studies there were no statements regarding the duration of either DAPT or TT, or what therapy was adopted once DAPT or TT was discontinued.

4. COMPOSITE ISCHAEMIC OUTCOMES

While it was common to report on a composite endpoint, the components of this endpoint differed across the 10 studies. In 7 studies adjusted composite endpoint results were given (Table 2). No individual study found a significant dif-

ference in composite end points between groups, although in 4 of the 7 studies there was a trend towards lower rates on TT (odds ratios ranged from 0.71 to 0.94) [11, 13, 17, 18].

5. MORTALITY

While all studies reported unadjusted mortality only three studies reported adjusted results for mortality (Table 2). In Mennuni *et al.* there was 8.6% 12 month mortality in the DAPT arm compared to a 7.1% rate on TT with an adjusted odds ratio of 0.62 [0.35-1.08] [18]. In Lamberts *et al.* the 12 month mortality rates for the DAPT and TT arms were 12% and 4% respectively, with adjusted all-cause mortality reduced with TT (OR 0.61 [0.47-0.77]) [11]. Ho *et al.* reported a 6.8% mortality on DAPT compared to 6.5% on TT, with an adjusted OR 0.96 [0.49-1.86] [17]. In

Table 1. Overview of included studies.

Study	Follow-up	Population	Design	Data Source	Groups	Allocation
Sambola <i>et al.</i> (2016) [9]	12 months	AF + PCI	Prospective	Hospital database	DAPT (n=266) TT (n=319)	Physician allocated
De Vecchis <i>et al.</i> (2016) [20]	378 ± 15.9 days	AF + PCI	Retrospective	Hospital database	DAPT (n=19) TT (n=48)	Physician allocated
Kang <i>et al.</i> (2015) [19]	20.6 ± 7.4 months	AF + DES	Retrospective	Hospital database	DAPT (n=236) TT (n=131)	Physician allocated
Mennuni <i>et al.</i> (2015) [18]	12 months	AF + PCI	Retrospective	Hospital databases	DAPT (n=488) TT (n=371)	Physician allocated
Rubboli <i>et al.</i> (2014) [15]	12 months	AF + PCI	Prospective	Hospital databases	DAPT (n=162) TT (n=679)	Physician allocated
Suh <i>et al.</i> (2014) [16]	42.0 ± 29.0 months	AF + PCI	Retrospective	Medical centre database	DAPT (n=166) TT (n=37)	Physician allocated
Fosbol <i>et al.</i> (2013) [13]	12 months	AF + NSTEMI with PCI	Retrospective	CRUSADE registry and insurance database	DAPT (n=1200) TT (n=448)	Not stated
Lamberts <i>et al.</i> (2013) [11]	12 months	AF + MI and/or PCI	Retrospective	Not stated	DAPT (n=3590) TT (n=1896)	Not stated
Ho <i>et al.</i> (2013) [17]	5.9 ± 5.0 months	AF + PCI	Retrospective	Not stated	DAPT (n=220) TT (n=382)	Not stated
Maegdefessel <i>et al.</i> (2008) [21]	16.8 (2-68) months	AF + PCI	Retrospective	Hospital database	DAPT (n=103) TT (n=14)	Not stated

Length of follow up is in months ± standard deviation or months (range); AF = atrial fibrillation; DAPT = dual antiplatelet therapy; DES = drug eluting stent; MI = myocardial infarction; NSTEMI = non ST elevation myocardial infarction; PCI = percutaneous coronary intervention; TT = triple therapy.

Table 2. Adjusted outcomes.

Study	DAPT Patients	TT Patients	Composite Endpoint	OR Composite	OR Mortality	OR Stroke	OR Bleeding
Sambola <i>et al.</i> (2016) [9]	N=266 79% ACS	N=319 68% ACS	Mortality, MI, stent thrombosis, repeat revascularisation	1.05 (0.67-1.86)	-	-	2.97 (1.25-7.02)**
Kang <i>et al.</i> (2015) [19]	N= 99 73.7% ACS	N= 99 76.7% ACS	Mortality, MI, repeat revascularisation, stroke	1.57 (0.82-2.99) †	3% DAPT vs. 7% TT†	0% DAPT vs. 4% TT†	6.84 (1.98-23.6)** †
Mennuni <i>et al.</i> (2015) [18]	N=488, 57% ACS	N=371, 54% ACS	Mortality, MI, stroke	0.77 (0.52-1.14)	0.62 (0.35-1.08)	4.4 (0.45-42.3)	1.79 (1.11-2.89)*
Rubboli <i>et al.</i> (2014) [15]	N=162, 66% ACS	N=679, 54% ACS	Mortality, MI, stent thrombosis, revascularisation, stroke	1.17 (0.57-2.5)	-	-	-
Fosbol <i>et al.</i> (2013) [13]	N=1200, 100% ACS	N=448, 100% ACS	Mortality, MI, stroke	0.94 (0.73-1.21)	-	-	1.29 (0.96-1.74)
Lamberts <i>et al.</i> (2013) [11]	N=3590, 72% ACS	N=1896, 53% ACS	MI, Coronary death	0.83 (0.68-1.0)	0.61 (0.47-0.77)*	0.67 (0.46-0.98)*	2.08 (1.64-2.65)*
Ho <i>et al.</i> (2013) [17]	N=220, 68% ACS	N=382, 71% ACS	Mortality, ischemic stroke, TIA	0.71 (0.37-1.38)	0.96 (0.49-1.86)	1.15 (0.21-6.35)	1.25 (0.6-2.6) ‡

Odds ratios (OR) are given relative to dual antiplatelet therapy (DAPT). Abbreviations ACS = acute coronary syndrome; MI = myocardial infarction; TIA = transient ischemic attack; TT = triple therapy. Statistically significant results are given by * $p < 0.05$, ** $p < 0.01$ *** $p < 0.001$. †=results were propensity-score matched, not adjusted; ‡ Bleeding odds ratio was for the subgroup of patients with a CHADS₂ score of greater than 2.

addition, Kang *et al.* reported propensity-score matched results and found a 3% mortality rate in the DAPT group compared to 7% in the TT group [19]. In the remaining studies Fosbol *et al.* reported mortality of 13.3% on DAPT versus 12.9% on TT without adjusted results being given [13], Suh *et al.* reported 11.4% mortality on DAPT, with no deaths in the 37 patients treated with TT [16], and Rubboli *et al.* reported 11% mortality rates in both groups [15]. Sambola *et al.* reported no difference in mortality with DAPT and TT arms with respect to patients with a CHA₂DS₂VASc of 1 (5.5% versus 7.4%, respectively) and those with CHA₂DS₂VASc of 2 or more (10.6% versus 9.2%, respectively) [9]. DeVecchis *et al.* reported 5 all-cause deaths, 1 in the DAPT group and 4 in the TT group [20] and Maegdefessel *et al.* reported 4 cardiovascular deaths, 3 in the DAPT group and 1 in the TT group [21].

6. STROKE

All 10 studies reported unadjusted stroke rates and these are given in Table 3. Stroke risk information (using CHADS₂ [22] or CHA₂DS₂VASc [23]) were given in 8 of these studies. In 2 of the studies the TT group had higher stroke risk than the DAPT group (Mennuni *et al.* CHADS₂ scores 2.9 versus 2.5, $p < 0.01$ [18]; Ho *et al.* CHADS₂ scores 2.6 vs. 2.1, $p < 0.001$ [17]), while in one the DAPT group had a higher stroke risk (Kang *et al.* CHADS₂ scores 2.06 vs. 1.68, $p = 0.003$) [19]. In the studies by Suh *et al.* [16], Rubboli *et al.* [15] and Fosbol *et al.* [13] the TT and DAPT groups had no statistical difference in their stroke risk. Lamberts *et al.* [11] and Sambola *et al.* [9] did not report statistical comparison of stroke risks between treatment arms, but data given appear similar.

DeVecchis *et al.* did not report stroke risk for the DAPT and TT arms, but reported 1 stroke event (2%) in the 48 patients in the TT arm and no strokes in the 19 patients in the DAPT arm [20]. Maegdefessel *et al.* also did not report stroke risk, and reported the highest stroke rate in the DAPT arm (8.7%), and reported no stroke in the 14 patients treated with TT [21].

In the other 8 studies the stroke rate varied between 0.2 and 5.3%. Of the 7 studies that performed statistical analyses only Sambola *et al.* reported significantly different stroke rates based on unadjusted results, with 5.3% in the DAPT group and 1.7% in the TT group ($p = 0.03$) [9, 13, 15-19].

Three studies presented adjusted results for stroke, with variable findings (see Table 2). Lamberts *et al.* reported that TT significantly reduced the risk of stroke compared to DAPT (OR 0.67, 0.46-0.98) [11]. Both Mennuni and Ho reported results favouring DAPT (OR 4.4 [0.45-42.3] [18] and OR 1.15 [0.21-6.35] [17] respectively), however neither of these results were statistically significant. In addition Kang *et al.* presented propensity-score matched stroke results, reporting no strokes in the DAPT group and 4% in the TT group [19].

7. BLEEDING

Different definitions of bleeding were used across the 10 studies (Table 4), and this resulted in differing rates of bleeding observed from a low of no bleeding to a high of 16.7% bleeding. Bleeding risk, using either HAS-BLED [24] or ATRIA [25] scores were reported in 7 of the 10 studies. In 5 of these studies there was no statistical difference in bleeding risk between treatment arms [13, 15, 16, 18, 19]. Lamberts *et al.* [11] and Sambola *et al.* [9] did not perform statistical

Table 3. Unadjusted stroke rates.

Study	DAPT Patients	DAPT Stroke Risk	DAPT Stroke Rate (%)	TT Patients	TT Stroke Risk	TT Stroke Rate (%)
Sambola <i>et al.</i> (2016) [9]	N=266 79% ACS	45% CHA ₂ DS ₂ VASc 2+	5.3*	N=319 68% ACS	56% CHA ₂ DS ₂ VASc 2+	1.7
DeVecchis <i>et al.</i> (2016) [20]	N=19 68% ACS	Not given	0	N=48 69% ACS	Not given	2
Kang <i>et al.</i> (2015) [19]	N=236, 77.4% ACS	Mean CHADS ₂ : 1.68*	2.1	N=131, 77.8% ACS	Mean CHADS ₂ : 2.06	3
Mennuni <i>et al.</i> (2015) [18]	N=488, 57% ACS	Mean CHADS ₂ : 2.5*	0.2	N=371, 54% ACS	Mean CHADS ₂ : 2.9	1.2
Rubboli <i>et al.</i> (2014) [15]	N=162, 66% ACS	Mean CHADS ₂ : 2.1	4	N=679, 54% ACS	Mean CHADS ₂ : 2.3	2
Suh <i>et al.</i> (2014) [16]	N=166, 43% ACS	65% CHADS ₂ 2+ Mean score: 1.95	3.6	N=37, 33% ACS	57% CHADS ₂ 2+ Mean score: 1.81	2.7
Fosbol <i>et al.</i> (2013) [13]	N=1200, 100% ACS	Median CHA ₂ DS ₂ VASc: 4	2.2	N=448, 100% ACS	Median CHA ₂ DS ₂ VASc: 4	1.6
Lamberts <i>et al.</i> (2013) [11]	N=3590, 72% ACS	90% CHA ₂ DS ₂ VASc 2+	4.2†	N=1896, 53% ACS	90% CHA ₂ DS ₂ VASc 2+	1.8
Ho <i>et al.</i> (2013) [17]	N=220, 68% ACS	Mean CHADS ₂ : 2.1*	0.9	N=382, 71% ACS	Mean CHADS ₂ : 2.6	1.1
Maegdefessel <i>et al.</i> (2008) [21]	N=103, 88% ACS	Not given	8.7†	N=14, 72% ACS	Not given	0

ACS = acute coronary syndrome; DAPT= dual antiplatelet therapy; TT = triple therapy. Statistically significant differences between treatment arms are indicated by * p <0.05. † statistical comparison of stroke rates not performed.

analysis however bleeding risk appears to be similar in both treatment arms.

Unadjusted bleeding rates were presented in all 10 studies and significant differences were observed in 3. Kang *et al.* reported a 16.7% bleeding rate in the TT group, significantly higher than the 4.6% in the DAPT group [19], and Mennuni *et al.* reported an 11.5% bleeding rate for TT group compared with 6.4% for DAPT [18]. Sambola *et al.* [9] also showed higher bleeding in the TT group (8.4%) when compared to the DAPT group (3.1%). Four studies (DeVecchis *et al.* [20], Rubboli *et al.* [15], Suh *et al.* [16] and Ho *et al.* [17]) did not find significant differences between bleeding rates while three studies (Fosbol *et al.* [13], Lamberts *et al.* [11] and Maegdefessel *et al.* [21]) did not perform statistical analyses on unadjusted bleeding rates.

Adjusted bleeding results were presented in 6 studies (see Table 1) and in 4 of these there was a statistically significant increase in bleeding associated with TT (Sambola *et al.* OR 2.97 [1.25-7.02], Kang *et al.* OR 6.84 [1.98-23.6], Lamberts *et al.* OR 2.08 [1.64-2.65] and Mennuni *et al.* OR 1.79, [1.11-2.89]). The other two studies reported non-significant increases in bleeding with TT (Fosbol *et al.* OR 1.29 [0.96-1.74], Ho *et al.* OR 1.25 [0.6-2.6]).

8. DISCUSSION

The quality of studies identified comparing clinical outcomes for patients with AF and ACS/PCI treated with DAPT or TT was poor. Eight of the ten studies included in this review were retrospective in nature, and none of the studies adequately described the basis of treatment allocation. Only one study was of a pure ACS population, the other nine containing a mix of stable coronary artery disease patients undergoing PCI and ACS patients. There was consistency in the observation that TT was associated with an increase in the rate of bleeding. While the largest study of the ten observed a reduction in stroke and in mortality associated with TT compared to DAPT, this was not a consistent finding.

This systematic review highlights a large gap in current literature, the lack of randomised control trials assessing treatment for patients with AF and ACS. Between 6 – 21% of patients with ACS may have concurrent AF, so this is a common clinical presentation [3]. In addition, a number of studies have shown that patients with AF have worse clinical outcomes following ACS than those without AF [26-28]. The absence of robust data on which to base treatment recommendations is therefore a significant concern. The latest ESC guidelines for NSTEMI-ACS had a number of treat-

Table 4. Unadjusted bleeding rates.

Study	DAPT Patients	DAPT Bleeding Risk	DAPT Bleeding Rate (%)	TT Patients	TT Bleeding Risk	TT Bleeding Rate (%)	Bleeding Definition
Sambola <i>et al.</i> (2016) [9]	N=266 79% ACS	HASBLED ≥ 3 , 37%	3.1*	N=319 68% ACS	HASBLED ≥ 3 , 42%	8.4	TIMI Major
DeVecchis <i>et al.</i> (2016) [20]	N=19 68% ACS	Not given	5.3	N=48 69% ACS	Not given	8.3	Major bleeding – not defined
Kang <i>et al.</i> (2015) [19]	N=236, 77.4% ACS	HASBLED, mean 2.1	4.6*	N=131, 77.8% ACS	HASBLED, mean 2.2	16.7	Intracerebral or hemodynamic compromise
Mennuni <i>et al.</i> (2015) [18]	N=488, 57% ACS	HASBLED, mean 2.9	6.4*	N=371, 54% ACS	HASBLED, mean 2.9	11.5	BARC 2+
Rubboli <i>et al.</i> (2014) [15]	N=162, 66% ACS	HASBLED, mean 2.9	12	N=679, 54% ACS	HASBLED, mean 2.9	10	BARC3 & 5
Suh <i>et al.</i> (2014) [16]	N=166, 42% ACS	HASBLED, mean 2.0	0.6	N=37, 33% ACS	HASBLED, mean 1.9	2.7	Overt bleeding, need for transfusion, intracranial bleeding
Fosbol <i>et al.</i> (2013) [13]	N=1200, 100% ACS	ATRIA, median 3	11.9†	N=448, 100% ACS	ATRIA, median 3	14.4	Bleeding causing hospital admission
Lamberts <i>et al.</i> (2013) [11]	N=3590, 72% ACS	HASBLED ≥ 3 , 24.3%	4.6†	N=1896, 53% ACS	HASBLED ≥ 3 , 24.3%	6.2	Bleeding causing hospital admission or death
Ho <i>et al.</i> (2013) [17]	N=220, 68% ACS	No bleeding risk score	9.6	N=382, 71% ACS	No bleeding risk score	10.6	Bleeding requiring transfusion
Maegdefessel <i>et al.</i> (2008) [21]	N=103, 89% ACS	No bleeding risk score	1.9†	N=14, 72% ACS	No bleeding risk score	0	Not defined in methods – requiring transfusion stated in results

ACS = acute coronary syndrome; BARC = Bleeding academic research consortium [48]; DAPT = dual antiplatelet therapy; TT = triple therapy. Statistically significant differences between treatment arms are indicated by * $p < 0.05$. † statistical comparison of stroke rates not performed.

ment recommendations for AF and ACS patients that had level of evidence C (expert opinion) [29]. The studies included in this review were all observational, mostly retrospective, and some very small. A number of these studies incorporated treatment groups other than DAPT and TT although these have not been discussed here. The original intent of this review had been to limit the studies discussed to pure ACS-AF populations. However, this would have left only the study by Fosbol *et al.* included [13]. The change to a mixed ACS and stable coronary disease inclusion expanded the number of studies included, but at the risk of altering the characteristics of the patient population. Treatment allocation was inadequately described in all studies. While consensus documents suggest stratifying patient by risk to determine treatment regimen [4, 7, 29], none of the studies included in this review have stated that this was done. The similarity in stroke and bleeding risk scores between the treatment arms in the majority of studies supports this notion. There are ongoing randomised trials such as REDUAL-PCI (dual therapy with dabigatran and either clopidogrel or ticagrelor, *versus* TT with warfarin, in patients with AF undergoing PCI) [30] and MUSICA-2 (DAPT vs. TT in patients with AF and low to moderate thromboembolic risk

undergoing PCI) [31] which when completed may provide more guidance regarding optimal pharmacological therapy, but none will directly address ACS patients with AF.

On the basis of the small number of studies in this systematic review it is evident that bleeding rates are significantly higher in patients treated with TT compared to DAPT. This was demonstrated consistently in the adjusted results, including the two largest studies, Fosbol *et al.* [13] and Lamberts *et al.* [11], with the former particularly pertinent as it was the only study to only include patients with ACS. Greater bleeding in TT groups was also supported in the majority of unadjusted results. There are some limitations that need to be noted here. Bleeding definitions used varied considerably, and the observed bleeding rates varied in part as a consequence of this. However, some of the studies that only included major bleeding reported higher rates of bleeding than others that had broader definitions of bleeding. It is possible that some bleeding was not captured in some of these studies due to the retrospective nature of most of the studies.

The bleeding results reported in this study are consistent with the data from randomised controlled trials conducted in ACS populations that have compared TT to DAPT. In AT-

LAS ACS 2-TIMI-51 patients were randomised to rivaroxaban low dose (2.5mg twice daily) or high dose (5mg twice daily) plus DAPT or DAPT alone [32]. This study reported a reduction in cardiovascular and all-cause mortality associated with the low dose of rivaroxaban (but not the higher dose) and an increase in non-CABG related major bleeding but not fatal bleeding in both TT groups. The APPRAISE-2 study examined the addition of apixaban (5mg twice daily) to DAPT. This study was halted prematurely as there was no evidence of a reduction in the composite end point of cardiovascular death, MI or ischaemic stroke associated with TT, and a significant increase in major bleeding was observed in the apixaban group [33]. A recent meta-analysis including the two phase III trials APPRIASE-2 and ATLAS ACS2-TIMI 51 and 5 phase II trials in ACS with DAPT and TT arms reported an increased risk of bleeding associated with TT (Hazard Ratio 2.34; 2.06-2.66) with a modest reduction in MACE (HR 0.87; 0.80-0.95) [34]. A similar association was described in a sub-study of the RE-LY trial, demonstrating that for warfarin and both 110mg and 150mg doses of dabigatran, addition of antiplatelet agents resulted in increased major bleeding [35]. Furthermore, nationwide registry data from Denmark of 40,812 MI patients showed that risk of bleeding causing hospitalisation increased with the number of antithrombotic drugs used, with those on TT at highest risk (compared to aspirin, DAPT HR 1.47 (1.28-1.69), TT HR 4.05 (3.08-5.33) [36]. Taking the results from these studies together with the findings in this review, it seems highly likely that TT in AF and ACS patients will result in an increase in clinically important bleeding.

The efficacy of TT was less clear in the studies reviewed here. It might have been expected that the major benefit of TT would be seen in a reduction in the rate of stroke. This is based on meta-analysis of AF studies, showing superiority of warfarin to antiplatelet therapy for the reduction in stroke [37]. Consistent with this, the largest study included in this review did observe a reduction in stroke associated with TT [11]. However the second largest study, Fosbol *et al.* reported a 2.2% rate of stroke on DAPT and a 1.6% rate on TT, which were not significantly different in unadjusted analysis. Three other studies reported a trend towards higher stroke rates on TT in adjusted analysis, although in none of these cases was a statistically significant result observed [17-19]. These results suggest that the benefits of adding warfarin to DAPT for stroke prevention in the context of ACS in AF patients is not clear.

It is also unclear that there is a reduction in composite ischaemic endpoints or in mortality associated with TT, although in the case of mortality Lamberts *et al.* did demonstrate a mortality advantage [11]. Whilst it is conceivable that addition of and OAC to DAPT may reduce mortality related to thromboembolic events [32], it is also clear that major bleeding events in patients with ACS are associated with an increase in mortality [38, 39].

The ESC AF guidelines of 2014 [8] include a structured algorithm based on stroke risk and bleeding risk to determine the combination of antithrombotic and antiplatelet therapy. The subsequent ESC NSTEMI-ACS guidelines of 2015 [29] present a simplified version that does recommend TT for all ACS patients undergoing PCI, for 1 month in those with

high bleeding risks and 6 months for those with lower bleeding risk, followed by dual therapy (clopidogrel and anticoagulation) out to 12 months. Bleeding risk in this context is defined by HASBLED[24], and while this score has been well validated in AF, it has not been validated in AF and ACS. The current ACC/AHA STEMI [40] and NSTEMI [41] guidelines both note the increased risk of bleeding associated with TT, and suggest that where this is warranted, an INR of 2.0 to 2.5 might be considered. The ACC/AHA guidelines do not reference a bleeding score. The studies included in the current review showed similar bleeding scores in both treatment arms suggesting that bleeding risk was not strongly associated with treatment allocation. In three studies there was a higher stroke risk in the TT arm, which may indicate stroke risk was a factor in treatment allocation in at least some cases.

Within the ESC guidelines [8, 29] the term OAC is used and refers to either well-controlled warfarin or one of the novel oral anticoagulants. It is important to note that all of the studies in this review that used oral anticoagulants were using a vitamin K antagonist (VKA), predominantly warfarin, and it is entirely possible that the use of novel oral anticoagulants would result in a different safety-efficacy ratio. Whilst there is lack of supporting evidence in this context, the superiority of the novel oral anticoagulants over warfarin for stroke prevention in AF patients has been demonstrated [42-45] and therefore the ESC suggestion of anticoagulation using these agents may be logical. Current ACC/AHA guidelines limit comment to warfarin on the basis that data is lacking for the newer agents [40]. With regard to DAPT therapy all of the studies in this review are referring to an aspirin and clopidogrel combination. The ESC guidelines advocate the use of aspirin and clopidogrel to constitute DAPT in the context of AF, but not the newer P2Y₁₂ receptor inhibitors prasugrel and ticagrelor, based on no proven benefit in the AF and ACS population. Both prasugrel and ticagrelor have both been shown to be superior to clopidogrel on the basis of the TRITON-TIMI 38 [46] and PLATO [47] trials respectively. However, these agents were both associated with increased risks of non-CABG related bleeding compared to clopidogrel. The absence of even observational data describing outcomes in AF and ACS patients treated with the newer anticoagulants and antiplatelet agents is striking and further demonstrates the paucity of data to guide clinical decision making in treating this group of patients.

This review has focused exclusively on the comparison of DAPT and TT. However, the combination of OAC and a single antiplatelet agent for AF and ACS patients may be important to consider. Lamberts *et al.* included both aspirin and warfarin, and aspirin and clopidogrel treatment arms in their study, and found both resulted in significantly less bleeding than TT, without any difference in rates of stroke [11]. The WOEST trial, examined OAC + antiplatelet (VKA + clopidogrel) to TT (VKA + clopidogrel + aspirin) in a slightly different population (69% AF and only 25-30% ACS). At 1 year follow-up significantly less total bleeding occurred in the oral anticoagulant plus clopidogrel group (HR 0.36, [0.26-0.50], p<0.0001), with no difference in major bleeding detectable. This reduction in bleeding was accompanied with a decreased rate of thrombotic events (com-

posite of MI, stroke, TVR and stent thrombosis) (HR 0.6, [0.38-0.94], $p=0.025$), and showed an all-cause mortality benefit over TT (HR 0.39, [0.16-0.93], $p=0.027$) [48]. The recently completed PIONEER AF-PCI study examined dual therapy (rivaroxaban and P2Y₁₂ inhibitor), *versus* TT with rivaroxaban or warfarin, in AF patients undergoing PCI, with about 50% of the patients having ACS. There was no DAPT arm in this study, so the study did not meet the inclusion criteria for our systematic review. The warfarin, aspirin, P2Y₁₂ inhibitor arm of this study had the highest bleeding rate, and the lowest bleeding rate was observed in the rivaroxaban-clopidogrel arm. The study was not powered to examine efficacy, and no difference in MACE between groups was reported [49]. While it is possible that some combination of novel OAC and a single antiplatelet agent may be superior to DAPT or TT, this is not currently recommended therapy within guidelines. Examining the utility of an oral anticoagulant and a single antiplatelet agent may therefore have merit. This area is now considerably more complex, as the novel oral anticoagulants and new antiplatelet drugs provide an increased range of possible therapeutic combinations, at a range of dosing options, that adds to the confusion in how best to treat AF patients with ACS.

9. STUDY LIMITATIONS

We excluded a number of studies that were based on populations on oral anticoagulant treatment at the time of an ACS event. These studies would have included mostly AF patients, mixed with a smaller proportion of patients with mechanical valves, DVT/PE or other indications for anticoagulation. Our rationale for this exclusion was that the non-AF patients included have quite a different risk profile, and that many patients with AF and ACS may not have been on an anticoagulant at the time of the ACS. We did choose to include studies that were not in pure ACS patients, as had we not done so, only one study would have been included in the review. Meta-analyses were not performed due to heterogeneity of eligible studies and absence of randomised control trials. Information regarding the duration of either DAPT or TT, or what default therapy was once DAPT or TT was discontinued was inadequately described in all studies; therefore we were unable to draw inferences about optimal duration of therapy on the basis of our results.

CONCLUSION

Optimal drug therapy in patients with AF and ACS is complex as both atherothrombotic and thromboembolic protection is required. The existing literature comparing DAPT to TT for this group of patients was poor in quality, consisting predominantly of retrospective studies with mixed ACS and PCI patients. There was a lack of detail on treatment allocation, and important differences in the clinical characteristics of DAPT and TT treatment arms were often not accounted for. Where adjusted results were presented, TT was consistently associated with an increase in bleeding risk, but there was not consistent evidence of reduced stroke, or reduced composite ischaemic endpoints associated with TT. This review has highlighted the need for prospective randomised control trials to define optimal therapy and improve outcomes in the AF and ACS population.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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