Triple Oral Antithrombotic Therapy in Atrial Fibrillation and Coronary Artery Stenting

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ABSTRACT

Patients with atrial fibrillation affected by an acute coronary syndrome have indications for oral anticoagulation and dual antiplatelet therapy with aspirin and a P2Y₁₂ adenosine diphosphate receptor inhibitor after coronary artery stenting. The concurrent use of all 3 agents, termed triple oral antithrombotic therapy, significantly increases the risk of bleeding. To date, there is a lack of evidence on the proper combination and duration of anticoagulant and antiplatelet agents in patients with indications for both therapies. As such, care has been guided by expert opinion, and there is wide variation in clinician practice. In this review, the latest evidence on the risks and benefits of triple oral antithrombotic therapy in patients with atrial fibrillation after coronary artery stenting is summarized. We discuss the clinical risk scores useful in guiding the prediction of stroke, bleeding, and stent thrombosis. Additionally, we highlight where additional evidence is needed to determine the proper balance of anticoagulant and antiplatelet agents in this patient population.

Introduction

The addition of a P2Y₁₂ adenosine diphosphate receptor inhibitor to aspirin (ASA), or “dual antiplatelet therapy” (DAPT), in patients after an acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) is the standard of care for the secondary prevention of cardiovascular events and death.¹ The most common reason for oral anticoagulant (OAC) use in this setting is prevention of ischemic stroke in atrial fibrillation (AF).² Combination DAPT and OAC use is known as triple oral antithrombotic therapy (TOAT). Approximately 5% of patients have indications for TOAT following PCI and stenting. These patients pose management challenges: Each component increases bleeding risk, but discontinuation of OAC may increase the risk of stroke, and stopping either antiplatelet agent may increase the risk of stent thrombosis, myocardial infarction (MI), and death. Thus, the best combination of ASA, clopidogrel, and/or warfarin is unclear. As AF is expected to increase in prevalence as the population ages,³ and newer antiplatelet and OAC agents are used more frequently, it is important to review the evidence and discuss mitigating the hazards of TOAT utilizing clinical prediction rules.

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Variability in Practice

The American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) give TOAT following ACS and stenting a class IIb, level of evidence (LOE) C recommendation, advising it may be considered but that there is a lack of evidence supporting its use.¹ Not surprisingly, there is considerable heterogeneity in the combinations of OAC and antiplatelet agents prescribed in practice. This was illustrated by a substudy of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines (CRUSADE) trial, which enrolled patients between February 2003 and June 2006 and found that in the subset of 1247 patients with AF who underwent coronary stenting, 60% were prescribed TOAT, 31% ASA + clopidogrel only, and 3% warfarin + ASA only.⁴ Furthermore, a survey conducted in 2011 of 168 members of the Society for Cardiac Angiography and Interventions (SCAI) found that in patients requiring bare-metal stents, 87% of interventionalists preferred TOAT for 1 month followed by ASA + warfarin thereafter. In patients receiving drug-eluting stents (DES), 47% of interventionalists preferred TOAT for 6 months, and the remaining were split among the other combinations of OAC and antiplatelet agents available.⁵

Pathophysiology

An understanding of the pathophysiology underlying ischemic events in AF and following ACS and stenting is required to deliver optimal patient care for individuals with both conditions. Most ischemic events in AF are due to systemic embolism of “red” (or red blood cell-rich)

thrombus from the left atrial appendage.⁶ The low-flow state of the left atrial appendage leads to vascular stasis, promoting activation of the coagulation cascade and formation of a fibrin-rich clot. Although acute atheroembolism does involve platelet activation, this in turn leads to marked thrombin-rich clot generation as a consequence.⁷ For these reasons, both the prevention and treatment of thromboembolic events in AF require adequate anticoagulation, either with heparin, warfarin, factor Xa inhibition, or a direct thrombin inhibitor.⁸ As an international normalized ratio (INR) of <2.0 is inadequate to prevent arterial thrombosis, studies comparing novel OAC agents with warfarin should quote the percentage of time in therapeutic range.

Ischemic events following ACS treated with PCI with stenting are more likely to be caused by “white” (or platelet-rich) thrombus, due to local endothelial injury, platelet activation and aggregation, and subsequent activation of the coagulation cascade. Although anticoagulation does defer some protection from ischemic events following ACS, DAPT prevents stent thrombosis and stent restenosis and is the current standard of care following stenting.^{1,9,10} Thus, patients with both AF and recent ACS with stent implantation require treatment for both conditions, requiring the physician to navigate the competing interests of prevention of stroke, stent thrombosis, and iatrogenic bleeding.

Evidence on Use of Triple Oral Antithrombotic Therapy

The use of OAC in AF and antiplatelet agents following ACS with or without stenting separately are informed by numerous trials. Table 1 lists the major studies in these areas and illustrates that, although there is plentiful evidence guiding the care of patients with either AF or ACS, there is a paucity of data on how to treat individuals with both conditions.

Efficacy

The completed studies of TOAT are mostly retrospective and observational.^{5,11–15} They are heterogeneous in design, indications for therapy, combinations and doses of antiplatelet agents and OAC, follow-up durations, and definitions of bleeding.^{2,5,11} For these reasons, 2 major meta-analyses have drawn different conclusions on the efficacy of TOAT.

Regarding cardiovascular outcomes, the meta-analysis by Zhao et al compared TOAT with DAPT after stenting and found that TOAT was associated with fewer major adverse cardiovascular events (MACE; composite of cardiac death, MI, stent thrombosis, or target-vessel revascularization [TVR]) after ACS (odds ratio [OR]: 0.60, 95% confidence interval [CI]: 0.42–0.86, $P = 0.005$).¹⁴ The best estimation of the magnitude of this lower rate was seen in Karjalainen et al, in which patients on TOAT had a lower rate of MI and stent thrombosis over those on OAC + ASA or clopidogrel, to a rate comparable to DAPT.¹⁵ Zhao et al also showed that TOAT was associated with lower all-cause mortality than DAPT (OR: 0.59, 95% CI: 0.39–0.90, $P = 0.01$).¹⁴ Conversely, in a meta-analysis by Gao et al comparing patients on TOAT with those not on TOAT (ie, all other combinations), lower rates of MI or mortality were not seen.¹³

Table 1. Major Studies of OAC and Antiplatelet Therapy in AF and ACS

AF Only	AF + ACS/Stent	ACS/Stent
Warfarin	Limited Evidence	Warfarin ± ASA
BAATF	WOEST	ASPECT I & II
AFASAK I & II		CHAMP
SPAF I, II, III		APRICOT-2
SPINAF		WARIS I & II
CAFA		DAPT
EAFIT		Clopidogrel
AFFIRM		CURE
ATRIA		PCI-CURE
DAPT		CREDO
Clopidogrel		COMMIT
ACTIVE A		CLARITY-TIMI 28
ACTIVE W		PCI-CLARITY
Novel OAC		CHARISMA
Ximelagatran (anti-IIa)		CURRENT-OASIS 7
SPORTIF I–V		PRODIGY
Dabigatran (anti-IIa)		Prasugrel
RE-LY		TRITON-TIMI 38
Apixaban (anti-Xa)		Ticagrelor
AVERROES		PLATO
ARISTOTLE		Novel OAC
Rivaroxaban (anti-Xa)		Ximelagatran (anti-IIa)
ROCKET-AF		ESTEEM
		Fondaparinux (anti-Xa)
		OASIS 5 & 6
		Darexaban (anti-Xa)
		RUBY-1
		Apixaban (anti-Xa)
		APPRAISE I & II
		Rivaroxaban (anti-Xa)
		ATLAS ACS I & II
Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, aspirin; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant. See online Appendix for full study names and references.		

Regarding stroke, in Gao et al, patients on TOAT experienced 71% less stroke compared with those not on TOAT (OR: 0.29, 95% CI: 0.15–0.58, $P = 0.0004$).¹³ Zhao et al showed a similar trend.¹⁴ Focusing on Karjalainen et al, TOAT did not appear to be associated with a lower risk of stroke compared with OAC + a single antiplatelet agent.¹⁵ Thus, depending on the comparison, data from these meta-analyses of observational data show that TOAT appears to be

as effective in prevention of stroke as OAC, and as effective in prevention of cardiovascular events as DAPT.^{13,14}

Bleeding Risk

Whereas observational studies of TOAT have drawn somewhat different conclusions on its efficacy, most agree its major hazard is bleeding. The rates of bleeding on different combinations of OAC and antiplatelet agents from large registry studies are compared in Table 2.^{16–19} Registry data suggest that TOAT is associated with greater bleeding risk, at a rate 2.02–4.62 compared with ASA, 2.15–2.80 compared with clopidogrel, 1.25–3.24 compared with DAPT, 1.44–4.03 compared with OAC, 1.02–2.35 compared with OAC + ASA, and 0.97–1.34 compared with OAC + clopidogrel. In line with this, data from the meta-analyses suggest TOAT carries a 2-fold greater risk of major bleeding when compared with DAPT (OR: 2.12, 95% CI: 1.05–4.29, $P=0.04$)¹⁴ and a 3-fold greater risk when compared with all other therapies (OR: 3.16, 95% CI: 1.81–5.52, $P<0.0001$).¹³ In a third meta-analysis, the incidence of major bleeding with TOAT was $5.1\pm 6.7\%$ at 30 days and $8.0\pm 5.3\%$ at 6 months.²⁰ In most cases, the site of most serious bleeds was the gastrointestinal tract.

Prospective Data

The prospective studies included in the above meta-analyses are summarized in Table 3.^{21–26} Recently published, the What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting (WOEST) trial was the first randomized controlled trial of TOAT.²⁷ The WOEST trial randomized 573 patients following PCI who had an indication for long-term OAC to TOAT (warfarin + clopidogrel 75 mg + ASA 80–100 mg daily) or double therapy (warfarin + clopidogrel 75 mg daily). Treatment duration was for a minimum of 1 month after bare-metal stents, or 1 year after DES. At 1 year, the primary endpoint of any bleeding event was seen in 19.4% of patients on double therapy and 44.4% of patients on triple therapy (hazard ratio [HR]: 0.36, 95% CI: 0.26–0.50, $P<0.0001$). Double therapy also reduced the secondary endpoint of a composite of stroke, death, MI, stent thrombosis, and TVR compared with TOAT (11.1% vs 17.6%; HR: 0.60, 95% CI: 0.38–0.94, $P=0.025$). When

analyzed separately, there was reduced all-cause mortality with double therapy (2.5% vs 6.3%; HR: 0.39, 95% CI: 0.16–0.93, $P=0.027$), albeit with a very small number of deaths (7 vs 18). These results suggest that a strategy of OAC + clopidogrel (without ASA) leads to less bleeding, does not increase cardiovascular events, and may lower mortality compared with TOAT.

Balancing Risk and Benefit

Given the risks, a one-size-fits-all treatment approach may not be best for patients with AF following ACS and stenting. Risk scores may be helpful when making decisions regarding individualized antithrombotic regimens.

Assessment of Stroke Risk

The most widely used score to predict stroke risk in AF is the CHADS₂ score (congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, prior ischemic stroke or transient ischemic attack [2 points]). Rates of hospital admission and death due to thromboembolism per 100 person-years range from 1.67 with a CHADS₂ score of 0 to 22.4 with a CHADS₂ score of 6.²⁸ The CHA₂DS₂-VASc score (CHADS₂ + vascular disease, age 65–75, female sex) improves the ability to stratify patients with low-risk or intermediate-risk CHADS₂ scores (0 and 1, respectively).²⁸ Table 4 summarizes the rates of thromboembolism and death in patients not on OAC according to CHA₂DS₂-VASc score and risk category.²⁸ The ACC/AHA guidelines recommend ASA in patients with a CHADS₂ score of 0, and ASA or OAC in patients with a score of 1, depending on bleeding risk. Oral anticoagulant therapy is advised with a CHADS₂ score ≥ 2 .⁶ However, the 2012 ESC guidelines no longer advise ASA, but rather no antithrombotic treatment, for a CHA₂DS₂-VASc score of 0 and OAC for a CHA₂DS₂-VASc score ≥ 1 .²⁹ The use of these scores in TOAT is gaining traction. A recent retrospective study of 602 patients with AF post-PCI suggested that the net benefit of TOAT outweighs bleeding risk at CHADS₂ >2 .³⁰

Assessment of Bleeding Risk

The HAS-BLED score (hypertension, abnormal renal or liver function [1 point each], stroke, bleeding history, labile INR, elderly [age >65 years], drugs or alcohol [1 point

Table 2. Major Registry Studies Comparing Bleeding on Combinations of Antiplatelet and OAC Therapy

Study	No. of Patients	Follow-up, y	Major Bleeding Risk, %						
			ASA	Clopidogrel	DAPT	OAC	OAC + ASA	OAC + Clopidogrel	TOAT
Buresly et al ¹⁶	21 443 ^a	1.8 ^b	3.2	NA	6.8	5.9	8.3	NA	8.5
Sørensen et al ¹⁷	40 812 ^a	1.3 ^b	2.6	4.6	3.7	4.3	5.1	12.3	12.0
Lamberts et al ¹⁸	11 480 ^c	1.0 ^d	7.0	6.6	7.0	7.0	9.5	10.6	14.2
Hansen et al ¹⁹	118 606 ^e	3.3 ^b	3.7	5.6	7.4	3.9	6.9	13.9	15.7

Abbreviations: AF, atrial fibrillation; DAPT, dual antiplatelet therapy; MI, myocardial infarction; NA, not applicable; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; TOAT, triple oral antithrombotic therapy.

^a Following acute MI. ^b Rates expressed as incidence of bleeding events resulting in hospitalization per patient-year or person-year. ^c Following acute MI or PCI. ^d Rates expressed as incidence of nonfatal and fatal bleedings resulting in hospitalization per 100 person-years. ^e Following first diagnosis of AF.

Table 3. Prospective Observational Studies of Combination OAC and DAPT

Study (Year, Design)	No. of Patients	Follow-up, Months	% With AF	TOAT Duration	Major Points
Rogacka et al ²¹ (2008, registry)	127 (all TOAT)	21 ± 19.8	59	5.6 ± 4.6 mo	4.7% MB, less TVR w/DES vs BMS (14.1% vs 26.8%); MB, mortality similar in DES vs BMS.
Rossini et al ²² (2008, registry)	204 (102 DAPT, 102 TOAT)	18	33 (67 of TOAT)	157 ± 134 d	Trend for more MB on TOAT vs DAPT (10.8% vs 4.9%, $P = 0.1$), MACE similar (5.8% vs 4.9%). INR >2.6 only predictor of MB; INR 2–2.5 lowered MB.
Sarafoff et al ²³ (2008, registry)	515 (209 DAPT, 306 TOAT)	24	78 (67 of TOAT)	Variable (median, 12 wk)	INR 2–2.5; TOAT or DAPT given based on bleeding and ischemic risks; similar rates of death, MI, ST, or stroke, and MB.
Gilard et al ²⁴ (2009, registry)	359 (2 groups, all given TOAT initially)	12	69 (63 of TOAT)	Group 1 (234 patients): TOAT for 22 ± 31 d, then DAPT; group 2 (125 patients): all TOAT	Trend toward decreased stroke in group 2 (3.0% vs 0.8%; $P = 0.2$), but significantly more bleeding in group 2 (6.4% vs 2.1%). More bleeding with femoral than radial catheter (10.3% vs 3.8%).
Sambola et al ²⁵ (2009, cohort)	405 (278 TOAT, 81 DAPT, 46 AS)	6	68 (65 of TOAT)	NA; 86% on TOAT at 6 mo	In patients with low TE risk, DAPT had the lowest bleeding risk (14.6% TOAT vs 11.8% AS vs 0% DAPT). CV-event risk was similar between groups (6.7% TOAT vs 11.8% AS vs 0% DAPT, $P = 0.126$).
Gao et al ²⁶ (2010, cohort)	622 (142 TOAT, 355 DAPT, 125 AS)	12	100	NA; 47% on TOAT ≥ 1 y	INR 1.8–2.5; TOAT reduced MACCE (8.8% TOAT vs 20.1% DAPT vs 14.9% AS); MB similar among groups (2.9% TOAT vs 1.8% DAPT vs 2.5% AS); TOAT had best net outcome (less MACCE + MB).

Abbreviations: AF, atrial fibrillation; AS, anticoagulant + single antiplatelet; BMS, bare-metal stent; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; INR, international normalized ratio; MACCE, major adverse cardiac and cerebral events; MACE, major adverse cardiac events; MB, major bleeding; MI, myocardial infarction; NA, not applicable; OAC, oral anticoagulant; ST, stent thrombosis; TE, thromboembolic; TOAT, triple oral antithrombotic therapy; TVR, target-vessel revascularization, w/, with.

each)) is the most validated and easiest-to-use bleeding-risk score in AF.³¹ Table 5 summarizes rates of bleeding stratified by HAS-BLED score.^{31,32} HAS-BLED has a real-world-use c statistic approaching 0.8³² and was shown to predict bleeding in patients on TOAT.³³ Additionally, HAS-BLED was shown to be predictive of cardiovascular events (HR: 1.51, 95% CI: 1.27–1.81, $P < 0.001$) and stroke (HR: 1.70, 95% CI: 1.28–2.26, $P < 0.001$) as a continuous variable. The incidence of both bleeding and CV events was higher with increased HAS-BLED score, and bleeding only significantly exceeded thrombotic events at HAS-BLED >4.³⁴

Using stroke and bleeding-risk scores in combination may prove useful when balancing risk-benefit. Although HAS-BLED should not be used on its own to exclude patients

from OAC, a score ≥3 indicates a high bleeding risk. Caution and regular review of OAC and antiplatelet use is advised in these patients. However, a recent study of 590 patients undergoing PCI with AF and a CHA₂DS₂-VASc score >1 found that even in patients with HAS-BLED ≥3, benefits of OAC still appeared to outweigh risk.³⁵

Assessment of Stent Thrombosis Risk

In conjunction with bleeding risk, disposition to stent thrombosis should guide the type of stent placed, in turn impacting the duration of DAPT, and OAC management. Risk scores that allow for the quantification of stent thrombosis risk include the DERIVATION (DES Real-World Incremental Value in the Era of Percutaneous Revascularization),

Table 4. Summary of Clinical Risk Scores for ST

Score	Definition	Risk
DERIVATION ³⁶	Baseline LVEF <50% (4 points)	ST risk within 2 y:
	ACS (3 points)	Low risk (<3), 0%
	Bifurcation lesion (2 points)	Int risk (3–6), 0.8%
	LAD as treated vessel (2 points)	High risk (>6), 3.6%
	≥2 DES implanted (2 points)	
HORIZONS-AMI/ACUITY ³⁷	Type of ACS	ST risk within 1 y:
	NSTEMI w/o ST deviation (1 point)	Low risk (1–6), 1.7%
	NSTEMI w/ST deviation (2 points)	Int risk (7–9), 2.8%
	STEMI (4 points)	High risk (≥10), 6.5%
	Baseline platelet count	
	<250 000 (0 points)	
	240 000–400 000 (1 point)	
	>400 000 (2 points)	
	No. of vessels treated	
	1 (0 points)	
	2 (1 point)	
	3 (2 points)	
	IDDM (2 points)	
	Aneurysm or ulceration (2 points)	
	Absence of early (pre-PCI) heparin ^a (1 point)	
	Current smoking (1 point)	
	Prior PCI (1 point)	
	Baseline TIMI flow grade 0/1 (1 point)	
	Final TIMI flow grade <3 (1 point)	
SYNTAX ³⁸	Online calculator available ^b	ST risk within 1 y ^c :
		Q1 (≤8), 1.4%
		Q2 (8–14), 2.2%
		Q3 (15–22), 5.0%
		Q4 (≥23), 5.9%

Abbreviations: ACS, acute coronary syndrome; DERIVATION, DES Real-World Incremental Value in the Era of Percutaneous Revascularization; DES, drug-eluting stents; HORIZONS-AMI/ACUITY, Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction/Acute Catheterization and Urgent Intervention Triage Strategy; IDDM, insulin-dependent diabetes mellitus; Int, intermediate; IV, intravenous; LAD, left anterior descending artery; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; Q, quartile; ST, stent thrombosis; STEMI, ST-segment elevation myocardial infarction; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; w/, with; w/o, without.

^a Includes IV heparin or LMWH. ^b Available at <http://www.syntaxscore.com>. ^c Broken down by quartiles (Q); Academic Research Consortium, any ST in patients with MI.

Table 5. CHA₂DS₂-VASC and HAS-BLED Scores and Event Rates

CHA ₂ DS ₂ -VASC		HAS-BLED	
Score	Event Rate ^a	Score	Event Rate ^b
0	0.66	0	1.13
1	1.45	1	1.02
2	2.92	2	1.88
3	4.28	3	3.74
4	6.46	4	8.70
5	9.97	5	12.50
6	12.52	6	—
7	13.96	7	—
8	14.10	8	—
9	15.89	9	—
Low (0)	0.66 ^a	Low (0)	2.66 ^c
Int (1)	1.45 ^a	Moderate (1–2)	5.54 ^c
High (≥2)	5.72 ^a	High (≥3)	8.11 ^c

Abbreviations: CHA₂DS₂-VASC, congestive heart failure, hypertension, age ≥75 y, diabetes mellitus, prior ischemic stroke or transient ischemic attack + vascular disease, age 65–75 y, female sex; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile INR, elderly, drugs or alcohol; INR, international normalized ratio; Int, intermediate; OAC, oral anticoagulation; TE, thromboembolic event. No validation studies have been done in patients with HAS-BLED ≥6.

^a Rate of hospital admission and death due to TE per 100 person-years at 10-year follow-up in 73 538 patients not on OAC.²⁸ ^b Rate of major bleeding per 100 person-years at 1-year follow-up in 3456 patients of the Euro Heart Survey, of which 65% were on OAC.³¹ ^c Rate of bleeding per 100 person-years at 1-year follow-up in a validation cohort of 44 771 patients on OAC.³²

HORIZONS-AMI/ACUITY (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction/Acute Catheterization and Urgent Intervention Triage Strategy), and SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) scores (Table 4).^{36–38} The DERIVATION score appears to be the easiest to use and boasts good prognostic accuracy for early, late, and very late stent thrombosis (c statistics of 0.75, 0.65, and 0.73, respectively).³⁶

Recommendations for Clinical Practice

The 2012 ACCF/AHA Unstable Angina/Non-ST-Segment Elevation Myocardial Infarction Guidelines advise that in patients with indications for TOAT, a lower target INR of 2–2.5 should be considered (class IIb, LOE C).⁹ The 2011 ACC/AHA/SCAI guidelines for PCI advise at least 12 months of P2Y₁₂ inhibitor therapy after ACS, regardless of stent type placed (class I, LOE A), but that if risk of bleeding outweighs the anticipated benefit from the recommended duration of P2Y₁₂ inhibition, earlier discontinuation of P2Y₁₂ inhibitor therapy is reasonable (class IIa, LOE C).¹ Stent choice should be guided by the patient's overall picture of stent-thrombosis risk, restenosis risk, ability to comply with

DAPT, and bleeding risk. Proton-pump inhibitor therapy is advised with a history of gastrointestinal bleeding (class I, LOE C) and may be considered in patients at high risk of bleeding (class IIa, LOE C), including patients on TOAT.

The use of bivalirudin, in combination with DAPT, is a reasonable alternative to the combination of unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor during primary PCI (class I, LOE B).^{9,10} The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial found that compared with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor, the use of bivalirudin was associated less major bleeding and lower 30-day all-cause mortality.³⁹ Thus, the use of bivalirudin in patients on TOAT may be considered if patients are on warfarin and the INR is below therapeutic range. Given the lower risk of bleeding, it may be reasonable to consider bivalirudin once the effect of the novel anticoagulant has worn off, but more data are needed before this can be officially recommended.

Following ACS and PCI, the ESC advises that TOAT may be considered in the short term (3–6 months), or longer in selected patients at low bleeding risk, followed by long-term therapy with OAC + clopidogrel (or, alternatively, ASA 75–100 mg daily), plus gastric protection with proton-pump inhibitors, H₂ antagonists, or antacids.⁴⁰ In patients with high risk of thromboembolism, uninterrupted OAC is preferred. When OAC is given with clopidogrel or low-dose ASA, the INR goal should be lowered to 2.0–2.5. Additionally, OAC + a single antiplatelet agent may be considered for 12 months, and patients with stable vascular disease may be considered for OAC alone. To reduce bleeding risk, radial access is preferred. Direct thrombin inhibitors and glycoprotein IIb/IIIa inhibitors should be avoided, and only used if INR <2, unless there is a thrombus load not amenable to catheter-based removal.

Additional measures to reduce bleeding have been embraced by experts.^{5,11} Because ASA increases the rate of bleeding in a dose-dependent manner,¹¹ consideration should be given to reducing ASA to low-dose (81 mg) at discharge. In the event of a major bleed, one may preferentially discontinue OAC or ASA, as the single greatest predictor of ST is premature discontinuation of thienopyridine therapy. As nonsteroidal anti-inflammatory drugs (NSAIDs) have antiplatelet properties, caution should be exercised when using NSAIDs in patients on TOAT; other analgesics (ie, acetaminophen) should be used instead. Additionally, elective surgery should be delayed for the duration of DAPT.¹¹

Future Directions

Optimizing the Duration of DAPT

In a combined analysis of the Correlation of Clopidogrel Therapy Discontinuation in Real-World Patients Treated With Drug-Eluting Stent Implantation and Late Coronary Arterial Thrombotic Events (REAL-LATE) and Evaluation of the Long-Term Safety After Zotarolimus-Eluting Stent, Sirolimus-Eluting Stent, or Paclitaxel-Eluting Stent Implantation for Coronary Lesions—Late Coronary Arterial Thrombotic Events (ZEST-LATE) trials, DAPT for >12 months following DES was not associated with

Table 6. Ongoing Prospective Studies of TOAT After Stenting

Trial	No. of Patients	Duration, mo	Comparison	Primary Endpoints
ISAR-TRIPLE (NCT00776633) ⁵⁴	600	9	TOAT for 6 wk vs 6 mo, then ASA + OAC	Composite death, MI, definite ST, stroke, major bleeding
MUSICA-2 (NCT01141153) ⁵⁵	304	12	TOAT vs DAPT	Composite of death, stroke, MI, ST, TE
AFCAS (NCT00596570) ⁵⁶	996	12	Registry	Major hemorrhagic and thrombotic/TE complications, including cardiac death
WAR-STENT (NCT00722319) ⁵⁷	1000	12	Registry	Major/minor bleeding, MACE (need for urgent revascularization, MI, death), arterial/venous TE

Abbreviations: DAPT, dual antiplatelet therapy; MACE, major adverse cardiac events; MI, myocardial infarction; OAC, oral anticoagulant; ST, stent thrombosis; TE, thromboembolic/thromboembolism; TOAT, triple oral antithrombotic therapy. Trial descriptions available at ClinicalTrials.gov. See online Appendix for full study names and references.

improved cardiovascular outcomes at a mean follow-up of 19.2 months.⁴¹ Likewise, results from Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) showed that 24 months of DAPT was not more effective than 6 months in reducing death, MI, or stroke, but significantly increased bleeding.⁴² Moreover, preliminary results from the Efficacy of Xience/Promus vs Cypher in Reducing Late Loss After Stenting (EXCELLENCE) study demonstrated that 6 months of DAPT was noninferior to 12 months for everolimus-eluting stents, but not sirolimus-eluting stents.⁴³ Conversely, a recent study of the National Heart, Lung, and Blood Institute Dynamic Registry found a lower 4-year rate of death or MI in patients on DAPT for 24 months compared with those not.⁴⁴ Ongoing trials aim to resolve these discrepancies, including the Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months DAPT After Drug-Eluting Stenting (ISAR-SAFE) trial⁴⁵ and the Dual Antiplatelet Therapy Study (DAPT Study).⁴⁶

With the more potent P2Y₁₂ inhibitors prasugrel and ticagrelor, it is possible that the need for ASA as a component of DAPT after DES may diminish. The upcoming GLOBAL-LEADERS trial (NCT01813435) will test a strategy of DAPT with ASA and ticagrelor for 1 month, followed by 23 months of ticagrelor alone, against clopidogrel or ticagrelor + ASA for 12 months, followed by ASA alone indefinitely.⁴⁷ If the strategy of a modern single antiplatelet agent proves more efficacious than DAPT, this may allow for simplified treatment regimens in patients who would otherwise have indications for TOAT.

Future improvements in stent design may also help limit the need for DAPT. Improving the safety profile of DES by decreasing neointimal hyperplasia, and lowering the risk of late ST, may be the next frontier of stent development.

Stents with biodegradable polymers, or no polymer at all, are being designed and may eliminate the need for DAPT beyond treatment for ACS.⁴⁷

Novel Antithrombotic Drugs

There are minimal data on the use of the novel anticoagulants in TOAT (Table 1). The Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) trial compared 2 doses of the direct thrombin inhibitor dabigatran with warfarin for the prevention of stroke and systemic embolism in patients with AF and ≥ 1 risk factor for stroke.⁴⁸ RE-LY found that dabigatran 150 mg twice daily reduced the risk of stroke or systemic embolism and had a similar rate of major bleeding compared with warfarin, whereas the lower-dose dabigatran 110 mg twice daily had similar rates of stroke or systemic embolism but a lower rate of major bleeding than warfarin.⁴⁸ Specifically, the improved bleeding profile of dabigatran 110 mg twice daily compared with warfarin was seen regardless of whether patients were also on no other antithrombotic drugs, on a single antiplatelet agent (rates of major bleeding per year of 4.6% for warfarin + single antiplatelet vs 4.3% for dabigatran 150 mg + single antiplatelet vs 3.8% for dabigatran 110 mg + single antiplatelet), or concurrent DAPT (6.3% for warfarin + DAPT vs 5.5% for dabigatran 150 mg + DAPT vs 5.4% for dabigatran 110 mg + DAPT).⁴⁹ It should be noted that of patients on antiplatelet agents in RE-LY, most were on a single agent rather than DAPT.^{48,49}

With regard to factor Xa inhibitors, in Rivaroxaban vs Warfarin in Nonvalvular AF (ROCKET-AF), rivaroxaban 20 mg daily was noninferior to warfarin in reducing thromboembolic events or mortality, and had a similar rate of major bleeding, although only approximately one-third of patients were on ASA, and very few on DAPT.⁵⁰ In the

Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial, apixaban 5 mg twice daily was more effective in reducing ischemic events and reduced mortality, major bleeding, and intracerebral hemorrhage compared with warfarin.⁵¹ However, only approximately one-third of patients were on ASA, and 1.9% on clopidogrel. In contrast, the Apixaban With Antiplatelet Therapy After ACS (APPRAISE-2) trial added apixaban 5 mg twice daily to standard DAPT after ACS, and found that TOAT did not reduce death or cardiovascular events, but did increase major bleeding (HR: 2.59, 95% CI: 1.50-4.46, $P = 0.001$).⁵²

A meta-analysis of 30 866 patients on novel OAC agents (dabigatran, ximelagatran, rivaroxaban, apixaban, or darexaban) combined with a single antiplatelet agent or DAPT found that a novel OAC + ASA reduced MACE (composite of all-cause mortality, MI, or stroke) when compared with ASA alone by 30% (HR: 0.70, 95% CI: 0.59-0.84), but increased bleeding (composite of major and nonmajor bleeding) by 79% (HR: 1.79, 95% CI: 1.54-2.09). Compared with DAPT, TOAT with a novel OAC decreased MACE by 13% (HR: 0.87, 95% CI: 0.80-0.95) but increased bleeding by 134% (HR: 2.34, 95% CI: 2.06-2.66).⁵³

If newer anticoagulant agents were to be used in TOAT, dabigatran 110 mg twice daily or apixaban 5 mg twice daily seem reasonable choices, given their lower rates of bleeding compared with warfarin in the AF trials to date. However, the US Food and Drug Administration has yet to approve dabigatran at the 110 mg twice-daily dose (but it is widely available worldwide outside the United States). Moreover, no prospective studies in large numbers of patients exist to define the safest treatment strategy. Given the lack of data, caution should be exercised when using these agents in TOAT.

In regard to ACS, although the more effective antiplatelet agents prasugrel and ticagrelor may be attractive alternatives to clopidogrel in patients at high risk of stent thrombosis, early data suggest these agents may increase bleeding risk. There is no published data on their use in TOAT, and, at this time, these agents cannot be recommended for this use.

Improving the Evidence Base

There are numerous opportunities for progress in this field. There is a need for further study of a lower INR goal (2–2.5) and shorter duration of DAPT. Moreover, as the novel anticoagulant and antiplatelet agents grow in use, it will be essential to perform registry studies of patients using these agents as a component of TOAT. The use of risk scores (such as HAS-BLED and DERIVATION) should be further validated in large registry studies in patients on TOAT. The knowledge gained may better inform the design of large randomized clinical trials, which should incorporate these clinical risk scores in devising an individualized treatment strategy. There are several ongoing studies evaluating different treatment regimens in patients with indications for TOAT, as described in Table 6.^{54–57}

Conclusion

Management of patients with indications for TOAT is challenging, as each component of TOAT increases the risk

of bleeding, but stopping any agent carries risk. After ACS and PCI, decisions on the type of stent placed, the proper balance of OAC and DAPT, and duration of TOAT should be guided by consideration of a patient's risk for stroke, bleeding, and stent thrombosis. The CHADS₂/CHA₂DS₂-VASc, HAS-BLED, and stent-thrombosis risk scores may guide care when risk is uncertain, although there has not yet been a clinical trial to evaluate their use in determining treatment strategies for patients on TOAT. Precautions such as tight control of INR (2–2.5), utilization of gastric protection, avoidance of concurrent NSAID use, and radial access for PCI may help limit periprocedural and long-term bleeding complications. Large, prospective trials are needed to validate the current recommendations and the use of newer anticoagulant agents as a part of a TOAT regimen. With a better body of evidence, a consensus on the proper use of TOAT will be reached, and patient care will improve in the process.

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