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REVIEWS

Triple Therapy in Hospitalized Patients: Facts and Controversies

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The use of triple therapy (warfarin plus dual antiplatelet therapy) has increased in recent years due to an aging population with a higher risk for atrial fibrillation, as well as the increased use of coronary stents for acute coronary syndromes. Triple therapy confers a higher bleeding risk than either warfarin or dual antiplatelet therapy alone. However, warfarin alone is inadequate for patients with indications for triple therapy because of an unacceptable risk of stent thrombosis, and dual antiplatelet therapy is inferior to warfarin for the prevention of ischemic strokes in patients with atrial fibrillation, mechanical valves, or intraventricular thrombosis. Hospitalists face the challenge of balancing the aforementioned risks; the optimal management of these patients requires knowledge of the relevant literature and expertise. In this paper, we review the current literature on antiplatelet and anticoagulant combinations in patients with atrial fibrillation and coronary stents in order to improve adherence to published guidelines and to reduce the risk of bleeding. *Journal of Hospital Medicine* 2011;6:537–545. © 2011 Society of Hospital Medicine

Dual antiplatelet therapy (DAPT) (aspirin plus a thienopyridine: clopidogrel or prasugrel) has become the standard treatment for patients with acute coronary syndromes (ACS) and after coronary stent placement (Table 1). Anticoagulant therapy with warfarin is indicated for stroke prevention in atrial fibrillation (AF), profound left ventricular dysfunction, and after mechanical heart valve replacement, as well as for treatment of deep venous thrombosis and pulmonary embolism (Table 2). It is estimated that 41% of the U.S. population over age 40 years is on some form of antiplatelet therapy,[6] and 2.5 million patients, mostly elderly, are on long-term warfarin therapy.[7] More specifically, 5% of patients undergoing percutaneous coronary interventions (PCIs) also have an indication for warfarin.[8] With widespread use of drug-eluting stents (DES), the need for a longer duration of DAPT, and the increased age and complexity of hospitalized patients, the safety and challenges of triple therapy (combined DAPT and warfarin) have become more important to the practice of hospital medicine. Triple therapy may increase hospitalization rates, as the risk of major bleeding is four to five times higher than with DAPT.[9–11] In contrast, DAPT is much less effective than warfarin alone in preventing embolic events in AF,[12] and warfarin alone or in combination with aspirin (ASA) is inadequate therapy to prevent stent thrombosis. Even fewer data exist on the efficacy and safety of triple therapy in patients with mechanical valves or left ventricular dysfunction.

Hospitalists commonly care for patients on triple therapy; certain indications are appropriate and supported from the available literature while others lack evidence. Knowledge of existing practice guidelines and of supporting research studies leads to optimal management of these complicated patients, and minimizes excessive morbidity from bleeding complications or thromboembolic events such as strokes and stent thrombosis.

In the first part of this article, we present the evidence that supports current recommendations for DAPT or warfarin in specific medical conditions. We also address controversies and unanswered questions. The second part of this review focuses on the available data and provides guidance on the optimal care of patients on triple therapy.

DUAL ANTIPLATELET THERAPY FOLLOWING ACUTE CORONARY SYNDROMES

Table 3 summarizes key randomized trials of DAPT versus ASA alone in several clinical scenarios. The addition of clopidogrel to ASA in patients with non–ST-elevation ACS reduced the risk of adverse ischemic outcomes in the clopidogrel in unstable angina to prevent recurrent events (CURE) trial,[15] as well as in its substudy, the PCI-CURE (patients with ACS who have undergone stenting).[17] In the main CURE study, the study groups diverged within the first 30 days after randomization and the benefit of DAPT persisted throughout the 12

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TABLE 1. ACC/AHA/SCAI Recommendations for the Use of DAPT After PCI and UA/NSTEMI[a]

Class Recommendations		Level of Evidence
DAPT after PCI/stenting[1]		
ASA		
Class I	ASA 325 mg/d after PCI for 1 mo (up to 6 mo depending on type of stent implanted) and then 75–62 mg/d indefinitely	B
Class IIa	ASA 75-325 mg/d indefinitely after brachytherapy unless risk of bleeding is significant	C
	In patients at risk of bleeding, a lower dose of 75-162 mg/d is reasonable after stent implantation	C
Thienopyridine		
Class I	Clopidogrel 75 mg/d after BMS for at least 1 mo and ideally up to 12 mo unless increased risk of bleeding (at least 2 wk)	B
	Clopidogrel 75 mg/d after DES for at least 12 mo if not at high risk for bleeding	B
	2009 focus update[2]: Clopidogrel 75 mg daily or prasugrel 10 mg daily for at least 12 mo after BMS or DES for ACS	B
Class IIa	Clopidogrel 75 mg/d indefinitely after brachytherapy unless risk of bleeding is significant	C
Class IIb	In patients with potential for lethal or catastrophic stent thrombosis, consider platelet aggregation studies and increase clopidogrel dose to 150 mg/d if <50% inhibition of platelet aggregation is seen	C
	Continuation of clopidogrel 75 mg/day beyond 12 mo is reasonable after DES	C
	2009 focus update[2]: consider continuation of clopidogrel or prasugrel beyond 15 mo after DES placement	C
DAPT for UA/NSTEMI without stenting[3]		
ASA		
Class I	Continue ASA (75 to 162 mg/d) indefinitely	A
Clopidogrel		
Class 1	Clopidogrel (75 mg/d) for at least 1 mo (A) and ideally for up to 1 y	B
Dipyridamole		
Class III	Dipyridamole is not recommended because it has not been shown to be effective	A

Abbreviations: ACC/AHA/SCAI, The American College of Cardiology/American Heart Association/ Society for Cardiac Angiography and Interventions; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; UA/NSTEMI, unstable angina/non–ST-elevation myocardial infarction; ASA, aspirin; BMS, bare metal stents; DES, drug eluting stents; ACS, acute coronary syndrome. [a] Superscript numbers refer to references. Class I: conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective. Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb, usefulness/efficacy is less well established by evidence/opinion. Class III: conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful. Level of evidence A: data derived from multiple randomized clinical trials or meta-analyses. Level of evidence B: data derived from a single randomized trial or nonrandomized studies. Level of evidence C: only consensus opinion of experts, case studies, or standard-of-care.

TABLE 2. Risk of Thromboembolic Events per Year for Patients With Atrial Fibrillation or Mechanical Valve[a]

Condition	Risk (%)
Atrial fibrillation (without anticoagulation)[4]	
Low-risk atrial fibrillation (CHADS2 score 0)	1.9
Intermediate-risk atrial fibrillation (CHADS2 score 1)	2.8
High-risk atrial fibrillation (CHADS2 score 2-6)	4–18
Mechanical heart valve[5,b]	
Mechanical heart valve (without anticoagulation)	8.6[c]
Mechanical heart valve (treated with ASA alone)	7.5[c]
Mechanical heart valve (treated with warfarin)	1.8[c]
Mechanical aortic valve (treated with warfarin)	1.1[c]
Mechanical mitral valve (treated with warfarin)	2.7[c]

Abbreviation: CHADS2, congestive heart failure, hypertension, age, diabetes, prior stroke or transient ischemic attack; ASA, aspirin. [a] Superscript numbers refer to references. [b] The risk of thromboembolic events are highest for caged ball valves, followed by tilting disc valves, followed by bileaflet valves. [c] This category includes all reported valve thrombosis, major embolism, and minor embolism.

TABLE 3. Randomized Clinical Trials of Dual Antiplatelet Therapy With Clopidogrel Plus Aspirin Versus Aspirin Alone[a]

Trial	Endpoints	Results
ST elevation MI		
CLARITY-TIMI[13]	Incidence of death, infarct-related artery occlusion, or recurrent MI	36% reduction (95% CI 24–47); $P < .001$
COMMIT[14]	Incidence of death, MI, or stroke	9% reduction (95% CI 3–14); $P < .002$
ACS without ST elevation		
CURE[15]	Incidence of death, MI, or stroke	20% reduction (RR 0.80 [0.72–0.90]); $P < .001$
Bare-metal stent placement		
CREDO[16]	Incidence of death, MI, or stroke	27% reduction (95% CI 3.9–44.4); $P < .02$
PCI-CURE[17]	Incidence of death, MI, or urgent TVR	30% reduction (RR 0.70 [0.50–0.97]); $P < .03$

Abbreviations: MI, myocardial infarction; CLARITY–TIMI 28, Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction; CI, confidence interval; COMMIT, Clopidogrel and Metoprolol in Myocardial Infarction; ACS, acute coronary syndromes; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; RR, relative risk; CREDO, Clopidogrel for the Reduction of Events During Observation; PCI–CURE, Analysis of CURE patients who underwent a percutaneous coronary intervention; TVR, target vessel revascularization. [a] Superscript numbers refer to references.

months of the study period. DAPT is also superior to ASA in patients with ST-elevation myocardial infarction (MI) (CLARITY–TIMI 28 and COMMIT trials).[13,14] On the basis of these findings, DAPT has become the standard of care for patients with ACS. The American College of Cardiology (ACC)/American Heart Association (AHA)[3] and the European Society of Cardiology[18] recommend ASA treatment indefinitely for patients with ACS whether or not they underwent PCI. Clopidogrel is recommended for at least 12 months following ACS, especially for patients who receive a coronary stent.

Despite the proven efficacy of DAPT in ACS, about 15% of patients die or experience reinfarction within 30 days of diagnosis.[19] The continued risk for thrombotic events could be due to delayed onset of platelet inhibition and to patient heterogeneity in responsiveness to therapy with ASA and/or clopidogrel.[20] Consequently, the optimum dose for clopidogrel and ASA following ACS is uncertain. The CURRENT-OASIS 7 trial evaluated the efficacy and safety of high-dose clopidogrel (600-mg loading dose, 150 mg once daily for 7 days, followed by 75 mg/d) versus standard-dose clopidogrel

(300-mg loading dose, followed by 75 mg/d) and ASA (75-100 mg versus 300-325 mg/d) in patients with ACS who were treated medically, with or without stenting.[21] In the overall study population as well as in patients who did not receive stenting, there was no significant difference in the combined rate of death from cardiovascular causes, MI, and stroke between patients receiving the high-dose and the standard-dose clopidogrel (4.2% vs 4.4%; $P = .37$) and high-dose versus low-dose ASA (4.2% vs 4.4%; $P = .47$). There were no significant differences in bleeding complications between the two clopidogrel treatment arms or between the high-dose and low-dose ASA groups.

The ACC/AHA guidelines recommend ASA, 75-162 mg/d indefinitely after medical therapy without stenting (class I, level of evidence: A)[3] and clopidogrel 75 mg/d for at least 1 month (class IA) and optimally for 1 year (class IB). Clopidogrel monotherapy is appropriate for patients with ACS who are unable to tolerate ASA due to either hypersensitivity or recent significant gastrointestinal bleeding.

As is the case after coronary stenting, interruption of DAPT soon after ACS may subject patients to high recurrence of cardiovascular events, although few data are available to support this observation. Interruption of DAPT due to bleeding complications or surgical procedures more than 1 month after ACS may be reasonable for a patient who did not receive a stent. Clinicians should restart DAPT after the surgical procedure once the bleeding risk becomes acceptable.

DUAL ANTIPLATELET THERAPY FOLLOWING CORONARY STENTING

Following Bare Metal Stents

Stent thrombosis occurs in approximately 20% of patients who receive bare metal stents (BMS) without DAPT[22]; the risk is highest in the first 30 days after implantation. The clinical presentation of stent thrombosis is often catastrophic: MI or sudden death occurs in over 60% of cases. DAPT reduces the incidence of stent thrombosis to a clinically acceptable level.[22]

In the ISAR trial of 517 patients treated with BMS for MI, suboptimal angioplasty, or other high-risk clinical and anatomic features,[23] patients were randomly assigned to treatment with ASA plus ticlopidine or ASA plus anticoagulation with heparin and warfarin. The primary endpoint of cardiac death, MI, coronary bypass surgery, or repeat angioplasty occurred in 1.5% of patients assigned to DAPT and 6.2% of those assigned to anticoagulant therapy (relative risk [RR], 0.25; 95% confidence interval [CI], 0.06-0.77). The PCI-CURE study evaluated patients who received BMS after ACS.[17] The primary endpoint was a composite of cardiovascular death, MI, or urgent target-vessel revascularization within 30 days of PCI. Long-term administration of clopidogrel (8 months) conferred a lower rate of cardiovascular death, MI, or any revascularization ($P = .03$), with no significant difference in major bleeding between the groups ($P = .64$). In the CREDO trial,[16] investigators evaluated 2116 patients undergoing PCI at 99 North American centers. Subjects received either a 300-mg loading dose of clopidogrel or placebo 3-24 hours before PCI. All patients then received clopidogrel 75 mg/d through day 28. For the following 12 months, patients in the loading dose group received clopidogrel, and those in the control group received placebo. All patients received ASA throughout the study. At 1 year, loading dose plus long-term clopidogrel therapy conferred a 27% RR reduction (3% absolute risk reduction) in the combined endpoint of death, MI, or stroke ($P = .02$).

Based on these trials, the ACC and AHA recommend clopidogrel (75 mg/d) for a minimum of 1 month and optimally 12 months after BMS (class 1B).[2] For patients at increased risk of bleeding, the ACC/AHA recommends a minimum of 2 weeks of clopidogrel. Although lifelong therapy with ASA is recommended, the optimal dose of ASA after BMS is unknown. However, on the basis of clinical trial protocols (no randomized data), guidelines recommend ASA 162 mg-325 mg/d for at least 1 month, followed by indefinite use at a dose of 75-162 mg. In patients for whom there is concern about bleeding, lower doses of ASA (75-162 mg) are acceptable for the initial period after stent implantation.

Following Drug-Eluting Stents

Drug-eluting stents have become the standard percutaneous treatment for patients with symptomatic coronary artery disease. In 2005, a sampling of 140 US hospitals indicated that 94% of patients treated with a stent received at least one DES.[24] Compared with BMS, restenosis and the need for revascularization are significantly less frequent. In contrast, unanticipated high rates of very late (>1 year) stent thrombosis have complicated DES.[25] Because of the potentially lethal consequences of stent thrombosis, several authors have questioned the long-term safety of DES[26–35] and examined the role of extended DAPT in reducing this delayed complication.[27,31,36] Although the initial pivotal randomized trials of DES mandated clopidogrel use for only 3 months after sirolimus-eluting stent and 6 months after paclitaxel-eluting stent,[37,38] current guidelines recommend DAPT for at least 12 months after DES placement for patients who are not at high risk of bleeding.[1]

Although multiple studies have confirmed the benefit of DAPT, controversy remains regarding the extended use for more than 1 year. The only randomized trial that addressed this issue was nonblinded and underpowered.[39] In this study of patients from two ongoing trials, the REAL-LATE and ZEST-LATE, extended duration DAPT (>12 months, median duration 19.2 months), did not reduce the incidence of MI and cardiac death.[39] The rate of the primary endpoint was less than 25% of that expected (underpowered), and

patients had already received clopidogrel for up to 24 months before enrollment.

The results from small, nonrandomized trials regarding this issue have been contradictory. Banerjee and colleagues studied 530 consecutive patients who underwent PCI (85% received a DES), were free of cardiovascular events for 6 months after PCI, and had follow-up available for >12 months.[26] In a multivariate analysis, clopidogrel use for ≥1 year was associated with lower mortality (hazard ratio [HR], 0.28; 95% CI, 0.14–0.59); this effect was independent of traditional cardiovascular risk factors, clinical presentation, and DES use. In a study at the Duke Heart Center[40] among patients with DES (n = 528) who were event-free at 12 months, continued clopidogrel use conferred lower rates of death (0% versus 3.5%; difference, −3.5%; 95% CI, −5.9% to −1.1%; $P = .004$) and death or MI (0% versus 4.5%; difference, −4.5%; 95% CI, −7.1% to −1.9%; $P < .001$) at 24 months. In the TYCOON registry,[35] patients with DES receiving clopidogrel for 2 years had a rate of stent thrombosis (0.4%) that was similar to those with BMS (0.7%) but significantly lower than patients with DES and 1-year DAPT (2.9%).

In contrast, Roy and colleagues[33] found that clopidogrel cessation at 12 months did not predict stent thrombosis, and Park and colleagues[32] reported that clopidogrel continuation beyond 1 year did not appear to decrease stent thrombosis or clinical events after DES implantation. Similarly, Stone et al.[34] performed a landmark analysis on the basis of the prospective, double-blind TAXUS-II SR, TAXUS-IV, and TAXUS-V trials. The authors found that thienopyridine use beyond 1 year after DES may reduce stent thrombosis over the subsequent 12-month period, but did not reduce rates of death and MI at 2 and 5 years after either DES or BMS.

Current guidelines recommend ASA 162-325 mg/d for at least 3-6 months, followed by treatment indefinitely at a dose of 75-162 mg daily. Clopidogrel, on the other hand, is given at 75 mg/d for at least 12 months.

WARFARIN AFTER ACUTE CORONARY SYNDROMES

Warfarin with different international normalized ratio (INR) goals alone or in combination with ASA has been evaluated after ACS. In an early trial, patients with recent (mean interval 27 days) MI were treated with warfarin alone versus placebo.[41] Warfarin conferred a relative risk reduction in mortality of 24% (95% CI, 4-44%; $P = .027$) at the expense of major bleeding rates of 0.6%/y. In the ASPECT trial,[42] moderate to high intensity anticoagulation after MI resulted in a 53% and 40% reduction in the relative risk of reinfarction (annual incidence 2.3% versus 5.1%) and cerebrovascular events (annual incidence 0.7% versus 1.2%), respectively. In the WARIS II[43] and ASPECT-2[44] trials, moderate intensity warfarin (INR 2.0-2.5) in combination with low-dose ASA, compared with ASA alone, reduced the composite occurrence of death or nonfatal reinfarction, as well as recurrent coronary occlusion after ST-segment elevation MI. High-intensity warfarin therapy alone (INR 3.0-4.0 for ASPECT, 2.8-4.2 for WARISII) reduced ischemic vascular events compared with ASA alone. Not unexpectedly, major bleeding episodes were more common among patients receiving warfarin.

No randomized trials have compared DAPT with warfarin plus ASA for patients with ACS who did not receive stents. The ACC/AHA guidelines recommend warfarin for secondary prevention following ACS (class IIb). High-intensity warfarin alone (INR 2.5-3.5) or moderate intensity (INR 2.0-2.5) with low-dose ASA (75-81 mg/d) may be reasonable for patients at high ischemic and low bleeding risk who are intolerant of clopidogrel (level of evidence: B). Fixed dose warfarin is not recommended by the ACC/AHA primarily on the basis of the Coumadin Aspirin Reinfarction Study (CARS) results. This study of patients following MI was discontinued prematurely because of a lack of incremental benefit of reduced-dose ASA (80 mg/d) combined with either 1 or 3 mg of warfarin daily when compared with 160 mg/d of ASA alone.

TRIPLE THERAPY FOR PCI AND ATRIAL FIBRILLATION

AF is the most frequent indication (70%) for long-term therapy with warfarin in patients scheduled for stent placement.[10] Clinical trials have shown that warfarin alone is superior to ASA, clopidogrel, or DAPT for prevention of stroke in patients with AF.[45,46] Although warfarin is indispensable in these settings, DAPT is similarly necessary after stent implantation. As triple therapy increases the risk of bleeding, the management of patients with AF and who have received stents remains controversial. This situation is particularly problematic among patients who have received DES and may benefit from extended DAPT. No randomized trials exist to clarify the optimal treatment in these patients; and the feasibility of such studies is questionable. Small, mostly retrospective, studies (Table 4) provide limited guidance on this issue; most studies focus on bleeding events rather than the cardiovascular efficacy of triple therapy. Because of these limitations, cardiovascular societies give IIb recommendation for either triple therapy or the combination of warfarin and clopidogrel in this setting and the level of evidence is C.[1,59,60]

In the largest study to date, Nguyen et al.[58] evaluated 800 patients who underwent stenting for ACS and were discharged on warfarin plus single antiplatelet agent or triple therapy as part of the GRACE registry. At 6 months, triple therapy conferred a significant

TABLE 4. Studies of Triple Therapy for Patients With Atrial Fibrillation and Coronary Stents

Author	Year	Type	No.	Major Bleeding, % (range)	Thrombotic Events	Comments
Studies of one group (triple therapy group)						
Orford et al.[47]	2004	Obs	66	4.5 (0.2–11.2)	N/A	Bleeding occurred only with suboptimal control of INR and/or pre-existing GI disease.
Porter et al.[48]	2006	Obs	180	1.6 (0.0–4.2)	N/A	Bleeding rates were acceptable with short-term TT after PCI.
Rubboli et al.[49]	2007	Obs	49	18 (4.4–36.9)	N/A	Most hemorrhages occurred during TT.
Rogacka et al.[50]	2008	Obs	127	4.7	N/A	One-half of bleeding episodes were lethal and 67% occurred within the first month.
Studies comparing triple therapy with dual antiplatelet therapy						
Mattichak et al.[51]	2005	Obs	82	21 vs. 3.5 ($P = .028$)[a]	Reinfarction (29% vs. 9%, $P = .15$)	TT did not reduce reinfarction after stenting for MI but increased rates of GI bleeding and transfusions.
Khurram et al.[11]	2006	Matched cohort	214	6.6 vs. 0 ($P = .03$)	N/A	Higher bleeding rates for TT than DAPT. INR range or ASA dosage did not influence the bleeding risk.
DeEugenio et al.[9]	2007	Matched cohort	194	OR 5.0 (1.4–17.8, $P = .012$)	N/A	ASA dose, age, sex, BMI, DM, hypertension, and procedural anticoagulant type or use did not influence risk of major bleeding.
Ruiz-Nodar et al.[52]	2008	Obs	426	14.9 vs. 9.0 ($P = .19$)	Mortality: OR 3.43 (1.61–7.54, $P = .002$)[b] MACE: OR 4.9 (2.17–11.1, $P < .01$)[b]	TT was associated with a nonsignificant increase in major bleeding but lower all-cause mortality and fewer MACE.
Sarafoff et al.[53]	2008	Prosp	515	1.4 vs. 3.1 ($P = .34$).	MACCE: OR 0.76 (0.48–1.21, $P = .25$)	No difference in MACCE or bleeding at 2 y. Stent thrombosis did not differ between groups.
Rossini et al.[54]	2008	Prosp	204	10.8 vs. 4.9 ($P = .1$)	MACE: 5.8% vs. 4.9% ($P = .7$)	INR was targeted to the lower range (2.0-2.5). No significant difference in bleeding rates for TT versus DAPT at 18 mo. Less bleeding for patients whose INR was within target (4.9 versus 33%, $P = .00019$). No significant differences in MACE between groups.
Uchida et al.[55]	2010	Obs	575	18 vs. 2.7 ($P < .001$)	MACE ($P = .108$)	No differences in MACE rates. More bleeding for patients on TT.
Studies comparing triple therapy versus dual antiplatelet therapy versus wararin and single antiplatelet agent						
Karjalainen et al.[10]	2007	Matched cohort	239	OR 3.3 (1.3–8.6, $P = .014$)[c]	MACE: OR 1.7 (1.0-3.0, $P = 0.05$)[c]	This study compared patients on warfarin at baseline with those not on warfarin—all undergoing stenting. Patients on warfarin at baseline were treated with a variety of strategies. Baseline warfarin use increased both major bleeding and MACE at 1 y. ASA plus warfarin was inadequate to prevent stent thrombosis, and premature warfarin cessation was associated with stroke.
Manzano-Fernandez et al.[56]	2008	Obs	104	EB (5.8 vs. 11.3, $P = .33$) LB (21.6 vs. 3.8, $P = .006$)[d]	MACE: 25.5% vs. 21.0% ($P = .53$)[d]	No difference in MACE rates between TT and non-TT (WAA or DAPT). TT conferred higher late bleeding (>48 h).
Gao et al.[57]	2010	Prosp	622	2.9 vs. 1.8 vs. 2.5 ($P = .725$)[e]	MACCE: 8.8% vs. 20.1% vs. 14.9% ($P = .010$)[e]	Target INR was set as 1.8-2.5. Lower stroke and MACCE rates for TT as compared with DAPT or WAA; no difference in bleeding.
Studies comparing triple therapy with warfarin and single antiplatelet agent						
Nguyen et al.[58]	2007	Obs	800	5.9 vs. 46 ($P = .46$)	Death: 5.1% vs. 6.5% ($P = .47$) Stroke: 0.7% vs. 3.4% ($P = .02$) MI: 3.3% vs. 4.5% ($P = .49$)	TT and WAA lead to similar 6-mo bleeding, death, and MI. Fewer strokes with TT (caveat: low event rate).

Abbreviations: Obs, observational; Pros, prospective; INR, international normalized ratio; GI, gastrointestinal; TT, triple therapy; PCI, percutaneous coronary intervention; MI, myocardial infarction; DAPT, dual antiplatelet therapy; ASA, aspirin; OR, odds ratio; BMI, body mass index; DM, diabetes mellitus; MACE, major adverse cardiovascular events; MACCE, major adverse cardiac and cerebral events; WAA, warfarin plus single antiplatelet agent; EB, early bleeding; LB, late (>48-h) bleeding. [a] Transfusions. [b] Dual antiplatelet therapy vs triple therapy. [c] Warfarin versus nonwarfarin. [d] Triple therapy versus non-triple therapy. [e] Triple therapy versus dual antiplatelet therapy vs warfarin and single antiplatelet agent.

reduction in stroke (0.7% versus 3.4%, $P = .02$) but not in death or MI. There were no differences in in-hospital major bleeding events between the two groups (5.9% versus 4.6%; $P = .46$). Similarly, Saraf-off et al.[53] reported no significant differences in the combined endpoint (death, MI, stent thrombosis or stroke) or bleeding complications among patients who received triple therapy or DAPT at 2 years of follow-up. In contrast, Ruiz-Nodar et al.[52] showed that triple therapy, compared with DAPT, at discharge reduced the incidence of death (17.8% versus 27.8%; adjusted HR = 3.43; 95% CI, 1.61–7.54; $P = .002$) and major adverse cardiac events (26.5% versus 38.7%; adjusted HR = 4.9; 95% CI, 2.17–11.1; $P = .01$), without a substantial increase in major bleeding events.

The value of combination antiplatelet therapy to prevent stent thrombosis in these patients is clearer in the study reported by Karjalainen et al.[10] This case-control study of 239 patients receiving warfarin at baseline who underwent PCI evaluated a primary endpoint of death, MI, target-vessel revascularization, or stent thrombosis and a secondary endpoint of major bleeding and stroke to 12 months of follow-up. Forty-eight percent of patients received triple therapy, whereas 15.5% were discharged on DAPT. The remaining patients received warfarin plus a single antiplatelet agent. Stent thrombosis occurred more frequently among patients receiving warfarin plus ASA (15.2%) than among those receiving triple therapy (1.9%). As expected, stroke was more frequent in patients treated with DAPT (8.8%) than among those receiving triple therapy (2.8%). Major bleeding was similar between groups. Therapy with warfarin was an independent predictor of both major bleeding and major cardiac events at 1 year. This observation illustrates that the outcome of PCI in patients on chronic warfarin therapy is unsatisfactory irrespective of the antithrombotic combinations used, highlighting the need for better strategies to treat these patients.

CHOICE OF THERAPY AND MANAGEMENT OF PATIENTS ELIGIBLE FOR TRIPLE THERAPY

Current guidelines for PCI do not provide guidance for patients with an indication for triple therapy due to a paucity of published evidence. Several ongoing prospective trials aim to address the management of these patients (AFCAS, ISAR-TRIPLE). Pending further study, clinicians should consider the embolic risk (CHADS2 score), target INR, type of stent, bleeding risk, and duration of treatment when determining the appropriate antiplatelet/anticoagulant combinations. The CHADS2 score (Table 2) stratifies the risk for stroke among patients with AF,[4] while the Outpatient Bleeding Risk Index (OBRI) allows estimation of bleeding risk.[12,61] The OBRI considers age > 65 years, prior stroke, prior gastrointestinal bleeding, and any of four comorbidities (recent MI, anemia, diabetes, or renal insufficiency) in order to stratify patients into three risk groups.[61] Patients with three to four risk factors have a high risk of bleeding (23% at 3 months and 48% at 12 months) whereas patients with no risk factors have only a 3% risk of bleeding at 12 months. Unfortunately, advanced age and prior stroke appear in both OBRI and CHADS.

For patients with AF who are at high risk for embolic stroke (>3% per year), we recommend triple therapy for the shortest time possible, followed by warfarin and ASA indefinitely. In case of BMS, it is acceptable to shorten triple therapy duration to 1 month. The optimal duration of triple therapy for patients with DES is uncertain; recommended durations range from 3 months to 1 year.[62] If the potential consequences of stent thrombosis are high due to a large amount of myocardium at risk, an extended period of triple therapy might be justified. For patients whose stroke risk is lower (CHADS2 score of 0-1), the risk for bleeding likely outweighs any benefit from stroke prevention. In this instance, it is reasonable to use DAPT with ASA and clopidogrel for 1 month after BMS and 12 months after DES, followed by ASA, with or without warfarin, indefinitely. In a recently published study, patients with AF and a CHADS2 score of 1 had a yearly stroke risk of 1.25% while taking DAPT[63]; the risk of major bleeding for triple therapy is 6.1% per year.[64]

For patients who have a high bleeding risk, BMS are the preferred stent type as the duration of triple therapy might be limited to 4 weeks. To our knowledge, no randomized study has evaluated the outcome of patients with BMS compared with DES who also have an indication for warfarin. Because studies have suggested that clopidogrel is more effective than aspirin in preventing stent thrombosis and in reducing death or MI after coronary stenting,[40,65] warfarin and single antiplatelet therapy with clopidogrel might be a reasonable treatment option in patients with high bleeding risk. The WOEST study (NCT00769938), currently recruiting participants, is the first randomized study specifically designed to test this hypothesis.

Since gastrointestinal bleeding accounts for approximately 30-40% of hemorrhagic events in patients on combined ASA and anticoagulant therapy, an expert consensus document recommended concomitant treatment with proton pump inhibitors (PPIs) to reduce this risk.[66] In contrast, the 2009 Focused Updates of the ACC/AHA/SCAI Guidelines did not recommend the use of PPIs with DAPT in the setting of ACS.[2] This is because of studies that show inhibition of platelet activation,[67] and potential clinical harm,[68] when clopidogrel is combined with certain PPIs that inhibit the CYP2C19 enzyme. However, to date there are no convincing randomized clinical trial data documenting an important clinical drug-drug interaction. The U.S. Food and Drug Administration (FDA) advises that physicians avoid the use of clopidogrel in patients with impaired CYP2C19 function due to known genetic variation or due to concomitant use of drugs that inhibit CYP2C19 activity. More specifically, the

FDA recommends avoiding the use of omeprazole and esomeprazole in patients taking clopidogrel.[69]

In particular, elderly patients have an increased risk of bleeding while receiving triple therapy. In a study of patients over age 65, 2.5% were hospitalized for bleeding in the first year after PCI, and the use of triple therapy was the strongest predictor of bleeding (more than threefold increase).[70] One in five patients suffered death or MI at 1 year after hospitalization for bleeding.[70] The basis for poor outcomes after hospitalization for bleeding in this population is multifactorial and may be due to the location of bleeding, associated hypercoagulable state, potential adverse impact of blood transfusion, withdrawal of warfarin therapy in patients with AF and PCI, and the premature discontinuation of DAPT. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is common among the elderly and conferred a doubling of bleeding risk.[70] Limiting the use of NSAID, the use of low-dose ASA beyond 30 days after stent implantation, greater use of BMS, and maintaining INR at the lowest possible level (INR of 2–2.5) will reduce the risk for bleeding.[57,71]

NEW ANTICOAGULANTS

Due to the high risk for bleeding with warfarin and the challenges inherent in INR monitoring, researchers have developed several novel anticoagulants whose advantages include fixed daily dosing and no need for monitoring. Dabigatran is a direct oral thrombin inhibitor that is already licensed in Europe and Canada for thromboprophylaxis after hip or knee surgery. It has also been studied in patients with AF. In the RELY trial, patients with AF who received dabigatran 110 mg daily had rates of stroke and systemic embolism that were similar to those with warfarin, as well as lower rates of major hemorrhage.[72] The randomized ReDEEM trial, reported at the AHA 2009 Scientific Sessions, was aimed at finding a dosage of dabigatran that achieves a good balance between clinical effectiveness and bleeding risk when combined with aspirin and clopidogrel after acute MI. Dosages ranging from 50 mg twice daily to 150 mg twice daily were all associated with 6-month rates of bleeding lower than 2%. Hospitalists should view these encouraging results cautiously until the publication of ReDEEM trial results in a peer-reviewed journal.

A variety of oral Xa antagonists are also being evaluated in patients with AF or ACS. These trials offer insight into triple therapy regimens that include ASA, clopidogrel, and an Xa antagonist. In a recent study of the oral Xa antagonist rivaroxaban, investigators stratified 3491 subjects with ACS according to whether they received concomitant ASA alone or ASA and clopidogrel.[73] Subjects receiving ASA plus rivaroxaban had a modest increase in bleeding. Triple therapy, however, increased the composite bleeding rate from 3.5% in the DAPT group to approximately 6-15% (low-dose or high-dose rivaroxaban, respectively). Rivaroxaban is currently under review by the FDA.

These novel agents might eventually replace warfarin for many or most indications for anticoagulation. It is imperative that future research compare the efficacy and risk of bleeding between triple therapy using these new agents and triple therapy with warfarin.

CONCLUSIONS

The management of patients on long-term anticoagulation who require DAPT because of ACS or coronary stenting is challenging. DAPT may safely substitute for warfarin only for patients at low risk for a thromboembolic event (ie, low-risk AF with low CHADS2 score). Clinicians should not interrupt warfarin in patients at higher risk (ie, intermediate to high-risk AF, mechanical valves, or recent venous thromboembolism), even in the presence of DAPT. In these patients, triple therapy is the optimal approach following coronary stenting (and possibly during the initial period after ACS without stenting). As this approach confers a fivefold increase in bleeding complications compared with DAPT, careful monitoring of the INR, the addition of PPIs, and the exclusion of elderly patients who are at the highest risk for bleeding complications[74] is recommended. The preferred duration of triple therapy after BMS in patients who require long-term anticoagulation is 1 month, whereas the optimal duration after ACS or DES remains unresolved.

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