

REVIEW

Triple Antithrombotic Therapy: Is it Time to Drop the Aspirin?

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KEY WORDS: aspirin; clopidogrel; oral anticoagulants; atrial fibrillation; acute coronary syndrome; drug-eluting stent; percutaneous coronary intervention

ABBREVIATIONS

ACS = acute coronary syndrome(s)
AF = atrial fibrillation
BARC = Bleeding Academic Research Consortium
BMS = bare metal stent
DAPT = dual antiplatelet therapy
DES = drug-eluting stent
HPR = high on-treatment platelet reactivity
MACCE = major adverse cardiac/cerebrovascular events
MI = myocardial infarction
NOACs = novel oral anticoagulants
OAC = oral anticoagulant(s)
PCI = percutaneous coronary intervention
VKA = vitamin K antagonist(s)

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ABSTRACT

Antithrombotic therapy is a continuously evolving field. However, as the number of available oral antiplatelet and anticoagulant agents continues to grow, so does the uncertainty regarding optimal combination therapy, as clinicians are increasingly faced with co-administration of therapies whose combined effects have not been fully evaluated. Perhaps, the most common and difficult of these scenarios is the use of dual antiplatelet therapy in patients who require chronic oral anticoagulation. Although each of these treatments has clear benefits, there is concern about the bleeding risk when they are used together, in the so called “triple therapy”. The obvious conflict raised by the prospect of triple therapy, is a more complete ischemic/ thromboembolic protection in the face of significantly increased bleeding risk and perhaps bleeding-related mortality. Accumulating data provide evidence to curtail triple therapy by omitting aspirin, when oral anticoagulation is needed for atrial fibrillation, while dual therapy with oral anticoagulation plus clopidogrel seems a safer and perhaps equally effective strategy compared with triple therapy.

INTRODUCTION

Antithrombotic therapy, defined broadly as pharmacological agents aimed at inhibiting components of either the coagulation (anticoagulants) or platelet aggregation cascades (antiplatelets), has served for decades as the therapeutic cornerstone in the management of many cardiovascular conditions including acute coronary syndromes (ACS) and acute myocardial infarction (MI), atrial fibrillation (AF), venous thrombosis and thromboembolism, in the setting of prosthetic heart valves and following percutaneous coronary intervention (PCI).

Aspirin is the most widely used antiplatelet agent. Low-dose aspirin has been shown to be effective in preventing about one-fifth of atherothrombotic vascular complications (non-fatal myocardial infarction, non-fatal stroke, or vascular death) in patients with previous MI, stroke, or transient cerebral ischemia. This corresponds to an absolute reduction of about 10–20 per 1000 patients in the yearly incidence of non-fatal events, and to a smaller, but still definite, reduction in vascular death.¹ Dual antiplatelet therapy (DAPT) most often comprises aspirin plus the thienopyridine, clopidogrel. Other approved oral antiplatelet agents, also being used in combination with aspirin, include the more potent thienopyridine, prasugrel and the cyclopentyl

triazalopyrimidine platelet inhibitor, ticagrelor.

Dual antiplatelet therapy with aspirin and clopidogrel or one of the newer agents interferes with platelet activation in complementary, but separate pathways. A number of randomized clinical trials have demonstrated and confirmed the incremental benefit and efficacy of DAPT above and beyond that of each antiplatelet agent alone. Data have also been obtained from studies where indications for the use of DAPT continue to expand into other patient groups, rendering and maintaining DAPT a sweeping combination in Cardiology.² Current guidelines for ACS and/or PCI broadly recommend the use of DAPT therapy after ACS, for 12 months irrespective of PCI, and after stent implantation for 4 weeks for a bare metal stent (BMS), or up to 12 months for a drug eluting stent (DES), in order to prevent stent thrombosis.^{3,4}

Long-term oral anticoagulants (OAC) are needed in patients with mechanical heart valves, AF at moderate to high thromboembolic risk, recent deep vein thrombosis or pulmonary embolism.⁵ Atrial fibrillation is the most common sustained cardiac arrhythmia, with rising prevalence with increasing age, reaching 9% in patients over 80 years, and is associated with a substantial risk of mortality and morbidity from stroke and thromboembolism. The most important consequence of AF is an increased risk of ischemic stroke, ranging up to a five-fold increased risk in patients with additional risk factors, summarized in the CHA₂DS₂-VASc score.⁶ Antithrombotic therapy is central to the management of AF patients, with OAC being recommended as thromboprophylaxis in patients at moderate–high risk of thromboembolism.^{5,6} While most anticoagulated patients are treated with vitamin K antagonists (VKA), oral anticoagulation with newer agents (either the direct thrombin inhibitor dabigatran or the direct factor Xa inhibitors, rivaroxaban or apixaban), is gaining popularity.

Approximately 70–80% of all patients in AF have an indication for continuous OAC, whereas coronary artery disease co-exists in 20–30% of them.^{6,7} Many of these patients are candidates for coronary revascularization, often in the form of PCI, usually including stent implantation. It has been estimated that 5–7% of patients undergoing PCI in the United States either have AF or another compelling indication for oral anticoagulation.⁸ As the prevalence of AF is strongly related to the age of patients and the mean age of patients undergoing PCI with stent implantation progressively becomes older, a growing pool of patients with overlapping clinical indications necessitating multiple antithrombotic agents is formed. The optimal antithrombotic management of these patients is still not well defined creating a dilemma for the treating physician.

TRIPLE THERAPY

The combined use of OAC and DAPT, is often referred to as “triple therapy.” One of the most common clinical sce-

narios requiring the use of triple antithrombotic therapy is the performance of PCI with stenting in a patient on OAC, usually due to AF. Owing to the superior efficacy of VKA, compared to DAPT with aspirin and clopidogrel, in preventing thromboembolic and thrombotic complications in patients with AF,⁹ and owing to the superior efficacy of DAPT compared to VKA, with or without aspirin, in preventing adverse cardiac events, following PCI with stenting,¹⁰ triple therapy with VKA, aspirin and clopidogrel is regarded as the optimal antithrombotic regimen in patients with an indication for VKA undergoing PCI.^{7,8} However, it is known that OAC and DAPT are each associated with nearly 15% risk of major or minor bleeding per year.⁹ As each regimen impairs hemostasis by a different mechanism, piling of antithrombotic therapy will result in an increased risk of bleeding. Meta-analysis data estimate the risk of major bleeding on triple therapy to be 2.2% at one month, increasing to as much as 12% at one year.^{11,12} While the exact magnitude of bleeding risk for any given population may be variable, the mortality hazard associated with large bleeds remains within a consistent range across studies. In stented patients, especially those undergoing PCI in the context of ACS or acute MI, major bleeding is associated with a several-fold increase in one-year mortality.^{13,14} In a recent pooled analysis of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) and Catheterization and Urgent Intervention Triage Strategy (ACUITY) trials, TIMI major bleeding was the single most predictive factor for long-term mortality (hazard ratio = 4.45) exceeding even those risks associated with MI or stent thrombosis.¹⁵ In this unfortunate subset of patients, the threat posed by bleeding is not only linked to the actual blood loss and the ensuing ischemic, hemodynamic and/or vascular sequelae, but also to the almost inevitable interruption or cessation of antiplatelet therapy. Additionally, some investigators have found an independent cardiovascular risk associated with transfusion therapy which persists even after propensity adjustment. On the other hand, discontinuation of either antiplatelet or anticoagulation therapy in this subset of patients may increase the risk of stent thrombosis and/or ischemic stroke, thus growing the uncertainty regarding optimal combination therapy.

CLINICAL STUDIES

Five meta-analyses reviewed the preferential use of triple therapy in patients on OAC undergoing PCI and stenting. They consistently reported a reduction in ischemic and thrombotic events, however counterbalanced by a twofold to threefold increase in major bleeding, thus diminishing these benefits.^{16–20} However, the included trials were small sized and mostly retrospective.

In 2010, a large Danish registry by Hansen et al²¹ consisting of more than 80 000 patients, further raised questions regard-

REMOVING ASPIRIN FROM TRIPLE ANTITHROMBOTIC THERAPY

TABLE 1. Recommended antithrombotic strategies following coronary artery stenting in patients with atrial fibrillation at moderate-to-high thrombo-embolic risk (in whom oral anticoagulation therapy is required).

Hemorrhagic risk	Stroke risk	Clinical setting	Recommendations
Low or moderate (HAS-BLED 0–2)	Moderate (CHA ₂ DS ₂ -VASc = 1 in males)	Stable CAD	At least 4 weeks (BMS), no longer than 6 months (DES): triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day ^a Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) ^b Lifelong: OAC ^c
	High (CHA ₂ DS ₂ -VASc ≥2)	Stable CAD	At least 4 weeks (BMS), no longer than 6 months (DES): triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day ^d Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) Lifelong: OAC ^c
	Moderate (CHA ₂ DS ₂ -VASc = 1 in males)	ACS	6 months: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) Lifelong: OAC ^c
	High (CHA ₂ DS ₂ -VASc ≥2)	ACS	6 months: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) Lifelong: OAC ^c
High (HAS-BLED ≥3)	Moderate (CHA ₂ DS ₂ -VASc = 1 in males)	Stable CAD	12 months: OAC and clopidogrel 75 mg/day ^b Lifelong: OAC ^c
	High (CHA ₂ DS ₂ -VASc ≥2)	Stable CAD	4 weeks: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day ^a Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) Lifelong: OAC ^c
	Moderate (CHA ₂ DS ₂ -VASc = 1 in males)	ACS	4 weeks: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day ^d Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) Lifelong: OAC ^c
	High (CHA ₂ DS ₂ -VASc ≥2)	ACS	4 weeks: triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day ^d Up to 12th month: OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day) Lifelong: OAC ^c

ACS: acute coronary syndrome; BMS: bare metal stent; CAD: coronary artery disease; DES: drug eluting stent; INR: international normalized ratio; OAC: oral anticoagulation, either VKAs (INR: 2.0–2.5) or non-VKA oral anticoagulant at the lower tested dose in AF (dabigatran 110 mg bid, rivaroxaban 15 mg od or apixaban 2.5 mg bid).

Proton pump inhibitors (PPIs) should be considered in all patients, particularly where aspirin is used. Newer generation DES should be preferred over BMS in patients at low risk for bleeding. (HAS-BLED 0–2).

^aCombination of OAC + clopidogrel 75 mg/day or dual antiplatelet therapy consisting of aspirin 75-mg/day and clopidogrel 75 mg/day may be considered as an alternative.

^bDual antiplatelet therapy consisting of aspirin 75 mg/day and clopidogrel 75 mg/day may be considered as an alternative.

^cAlone or combined with single antiplatelet therapy only in very selected cases (e.g. stenting of the left main, proximal bifurcation, recurrent MIs, etc). Standard intensity anticoagulation with either VKAs (target INR 2-3) or NOACs (standard dosing, unless other indications for reduced dose are present).

^dCombination of OAC and clopidogrel 75 mg/day may be considered as an alternative.

ing the true efficacy and safety profile of triple therapy. This large registry investigated bleeding complications in different antithrombotic strategies reporting the highest bleeding risk for triple therapy (hazard ratio - HR 3.70 for triple therapy vs OAC; HR 1.66 for DAPT vs OAC), thus providing support to the earlier findings of prior meta-analyses. Current guidelines endorse the use of triple therapy with the remark of using it for as short as possible. However, it has been found that even this approach is not without hazards. In 2011, the registry of Lamberts et al²² consisting of 11 480 patients found that AF patients following MI or PCI are at immediate risk of clinically significant bleeding with recommended triple therapy use. Within 30 days after initiation of triple therapy, crude incidence rates were 22.6 and 14.3 major bleeding events per 100 person-years for triple therapy and DAPT, respectively. During 12 months of follow-up, the highest bleeding rates persisted with triple therapy (14.2 vs DAPT 7.0 events per 100 person-years). The overall trend was a decrease in bleeding risk over time, but the initial elevated bleeding risk associated with triple therapy sustained over time when compared to less intensive antithrombotic regimens, thus indicating no safe therapeutic window of triple therapy with respect to bleeding risk. This registry reported an expected favourable effect with triple therapy on crude incidence rates of the combined endpoints of cardiovascular death, MI, and stroke, but the combination of OAC and a single antiplatelet agent actually seemed to perform similarly. This finding made a heretofore clear benefit in thrombosis protection with triple therapy compared with OAC plus single antiplatelet highly questionable. However, this finding can also be regarded as a footing for a possible new treatment regimen, being the combination of OAC and clopidogrel.

The What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (WOEST) study was the first trial aiming to simplify the antithrombotic management in patients requiring triple therapy, by removing aspirin from the antiplatelet therapy strategy.²³ WOEST was a prospective, randomized, controlled trial (n=573), assessing the hypothesis that the combination of OAC and clopidogrel 75 mg/day is safe and superior to triple therapy treatment in patients on chronic OAC undergoing PCI, with respect to the prevention of thrombotic complications, because of a reduction in bleeding risk. The study had few exclusion criteria, with the aim of reflecting a real-world-type population. The primary outcome was the combination of TIMI and GUSTO minor and major bleeding events up to 30 days and 1 year. The secondary outcomes were major adverse cardiac events. The WOEST trial clearly proved that dual therapy (OAC and clopidogrel, without aspirin) compared to triple therapy significantly reduces bleeding complications after coronary stenting (HR 0.36, 95 % confidence interval - CI 0.26–0.50, p<0.0001). Additionally, mortality at 1 year, a secondary endpoint, was significantly lower with double

therapy than with triple therapy (HR 0.39, 95% CI 0.16–0.93, p=0.027). By omitting aspirin in a high-risk population, a large reduction (>50 %) in the occurrence of any bleeding complication was achieved. It was anticipated that withholding aspirin would especially reduce the occurrence of gastrointestinal bleeding, possibly due to the local erosive effect of aspirin, which eventually turned out to be true. However, these low bleeding rates can be considered as highest, because more bleeding could have been prevented if proton-pump inhibitors and radial access for PCI were used more in this study. Surprisingly, the reduced bleeding rate was not counterbalanced by more thromboembolic events (OAC and clopidogrel vs triple therapy HR 0.60, 95 % CI 0.38–0.94, p=0.025). As thrombin is a strong platelet activator, it was hypothesized that the combination of thrombin inhibition by OAC and P2Y12 inhibition by clopidogrel makes COX-1 inhibition less relevant for protection of thrombotic and thromboembolic events. This hypothesis was based on the results of two large randomized trials,^{24,25} comparing OAC to aspirin in the prevention of re-infarction and stroke in patients surviving from MI. OAC was shown to be superior to aspirin, although associated with more bleeding. These studies strongly suggested that in coronary artery disease, full intensity OAC is at least as good as aspirin in protecting patients from thrombotic events. On the basis of these findings, aspirin does not need to be used in patients receiving oral anticoagulants and undergoing PCI.

There are some limitations regarding the results of the WOEST trial. First, although the rate of bleeding events overall was clearly reduced in the double-therapy group, the frequency of major bleeding episodes, as defined by the TIMI and GUSTO criteria, did not differ significantly between treatment groups. When minor and moderate bleeding episodes were assessed, however, including the Bleeding Academic Research Consortium (BARC) criteria,²⁶ a difference in favour of the double-therapy group was seen; the risk of adverse events related to minor bleeding is recognized.²⁷ Second, the trial adopted a more aggressive antiplatelet regimen than is recommended in guidelines; more than 70% of patients received clopidogrel for 1 year, and most patients received dual antiplatelet treatment for more than 6 months. This approach could have increased the frequency of bleeding episodes, but was adopted mainly because the investigators chose to use DES rather than BMS. Proton-pump inhibitors were used in only 34–39% of patients, and radial access was used in only 25–27%. Third, the study was underpowered to resolve with confidence that there is no excess of stent thrombosis when aspirin is omitted. Despite the clear limitations, the results of the WOEST trial provided support for reducing bleeding events by omitting aspirin in patients on chronic OAC undergoing coronary stenting.

A recently published Danish registry delivered strong numbers confirming the findings in WOEST trial. Lamberts et al²⁸ used national databanks and registries in Denmark to

explore the safety and efficacy of different anticoagulation regimens in patients with AF who also had MI and/or PCI. Their analysis has the advantage of studying outcomes in a large “real world” population, not one highly selected by rigorous inclusion criteria of a randomized trial. With this approach 12 165 AF patients, who were hospitalized for MI and/or PCI, were identified. Anticoagulation regimens were monotherapy in 38% (aspirin, clopidogrel, or OAC), dual therapy in 47% (dual antiplatelets or OAC + 1 antiplatelet), and triple therapy in 15%. Outcomes assessed after 1 year included MI, ischemic stroke, mortality, and bleeding, as judged from hospital stay and death records. In this analysis, OAC + clopidogrel emerged as the favored overall strategy. Compared with triple therapy, this dual combination showed no excess of MI or coronary death, and there was no difference in ischemic stroke or overall mortality. In terms of bleeding, OAC + clopidogrel showed a non-significant benefit compared with triple therapy. Other regimens, such as OAC + aspirin or dual antiplatelet therapy without OAC, were associated with less bleeding but at the cost of higher all-cause mortality rates. Not surprisingly, there were also more strokes among those treated with dual antiplatelets compared with any regimen that used an OAC. Those who had PCI without MI had a lower coronary event rate, but there was still a benefit for OAC + clopidogrel compared with the other regimens in these lower-risk patients. Other interesting findings were high subsequent mortality, MI, and stroke among those hospitalized for bleeding compared with those without. The higher rates of thrombotic events among those with nonfatal bleeding suggest that bleeding is dangerous not only because of the hemorrhage itself but also because it forces discontinuation of needed anticoagulation.

The Danish registry study had certain limitations. As with any retrospective registry, some important data might not be available. For example, this study does not inform us how many PCI patients had DES. Also, registry studies that use hospital diagnosis codes depend heavily on the accuracy of the coding. Fortunately, the codes employed in this study had been previously validated with relatively high specificities and predictive values. Another limitation of this study design is the possibility that treatment decisions were confounded by many clinical features that cannot be captured from the national databases. The authors acknowledge this important limitation and report that baseline characteristics, such as CHADS₂ and HAS-BLED scores, seem not to have influenced the choice of anticoagulation prescriptions. But it should be acknowledged that even this analysis does not control for other comorbidities that might lead physicians to choose a particular anticoagulation regimen (clopidogrel alone vs the combination of aspirin + clopidogrel) after a new cardiac event. In addition, the number of patients who were initially prescribed the “optimal” regimen of OAC + clopidogrel was relatively small (548 of 12 615 subjects). Moreover, this study did not address the time course of triple or even dual therapy after MI or PCI. Finally,

patients with MI in the previous year and therefore an even higher risk for thrombotic events in whom coronary protection with triple therapy outweighs the bleeding risks, were excluded from the Danish study. However, together with the WOEST trial, the Danish registry delivers strong evidence supporting double therapy (OAC + clopidogrel) without aspirin in the treatment of patients on chronic OAC undergoing elective or ACS-driven PCI as a safer and perhaps equally effective strategy compared with triple therapy.

Seivani et al²⁹ analyzed long-term safety and efficacy parameters in patients with AF, treated with a dual therapy (OAC plus clopidogrel) after PCI with stent implantation for a period of 6–12 months followed by monotherapy with OAC. Between January 2008 and August 2010, 221 patients with high-risk AF received a DES and a dual therapy with OAC and clopidogrel and were retrospectively identified. Efficacy endpoints included cardiac death, MI, stent thrombosis and cerebrovascular stroke at follow-up, while safety was assessed by bleeding events defined by the BARC criteria. The mean follow-up period was 19 months with a mean duration of dual therapy of 9 months. Nearly half of patients continued OAC during PCI, which has been reported to result in less bleeding complications than bridging therapy with heparin. The rate of bleeding was 10% at 19 months of follow-up, and more than half of these (5.45%) were procedure related. Similar to these lower bleeding events, when comparing this study with WOEST, 12-month survival estimates for MI (2.2 vs 3.2%), stent thrombosis (0.6 vs 1.4%), stroke (1.4 vs 1.1%), and target vessel revascularization (12.2 vs 7.2%) were lower, whereas overall death was higher (3.7 vs 2.5%) in this study than that in dual therapy arm of WOEST. Like WOEST, Seivani et al further confirmed that dual therapy with OAC and clopidogrel after PCI with stent implantation is safe and effective in a high-risk AF cohort. Moreover, they suggest that cessation of a P2Y₁₂ inhibitor after a mean duration of 9 months and proceeding only with OAC is appropriate provided that target INR is maintained.

The efficacy and safety of antithrombotic regimens for patients with AF undergoing PCI was assessed in another registry. The AFCAS (Atrial Fibrillation Undergoing Coronary Stenting) trial, was a prospective non-randomized study.³⁰ Consecutive AF patients undergoing PCI with stent implantation at 17 European institutions were included and followed for 1 year. Out of the 975 patients enrolled, 914 were included in the final analysis. The mean CHADS₂ score was 2.2 ± 1.2 , and 71% of patients had a CHADS₂ score ≥ 2 . Triple therapy of VKA, aspirin, and clopidogrel was prescribed to 74% of patients, dual antiplatelet therapy to 18%, and VKA plus clopidogrel to 8%. In contrast with most of the previous literature consistently showing that triple therapy is associated with less major adverse cardiac/cerebrovascular events (MACCE), but more bleeding compared to other antithrombotic regimens, comparable efficacy and safety of triple therapy, DAPT and

VKA+clopidogrel was observed at 1-year follow-up, even when adjusted for propensity score. These findings are in accordance with the data derived from the Danish registry,²⁸ where a comparable overall efficacy of triple therapy, DAPT, and VKA+clopidogrel on the occurrence of MACCE in AF patients undergoing PCI with stenting and a non-significantly greater risk of bleeding, with triple therapy compared to VKA+clopidogrel, has been reported. The contrasting observation of a large and significant reduction in the incidence of bleeding with VKA+clopidogrel compared to triple therapy reported in the WOEST study,²³ was attributed by the authors, to methodological features. The observational, open-label design and the small size of some treatment groups, particularly the group receiving VKA+clopidogrel, are among the limitations of this study.

The combination of oral anticoagulants plus aspirin without clopidogrel or aspirin plus clopidogrel without oral anticoagulants has not been extensively studied. However, in patients with AF assessed in the ACTIVE-W study,⁹ full intensity oral anticoagulation protected better against ischemic complications than double antiplatelet therapy with aspirin and clopidogrel. Withholding oral anticoagulation in patients with AF undergoing PCI is associated with increased major cardiovascular events and mortality, and does not seem to reduce bleeding,^{10,31} and the omission of clopidogrel in patients receiving coronary stents has been associated with an increased risk of thrombotic events, such as MI and stent thrombosis.^{10,32} Therefore, only the option of combining oral anticoagulants with clopidogrel seems feasible.

Recently the results of ISAR-TRIPLE (Testing of a Six-week Versus a Six-month Clopidogrel Treatment Regimen in Patients With Concomitant Aspirin and Oral Anticoagulant Therapy Following Drug-eluting Stenting) trial were announced in a major meeting.^{33,34} The ISAR-TRIPLE trial, was a randomized, open-label trial that examined the restriction of clopidogrel therapy from 6 months to 6 weeks after DES implantation in the setting of concomitant aspirin and oral anticoagulant. A total of 614 patients undergoing implantation of a DES at 3 European centers were randomized in a 1:1 fashion. All patients were treated with aspirin and a VKA and randomized to 6 weeks or 6 months of clopidogrel therapy. The primary end point was a composite of death, MI, definite stent thrombosis, stroke, or major bleeding. The secondary end point comprised ischemic and bleeding complications. Clinical follow-up was scheduled at 6 weeks and at 6 and 9 months after randomization. Regarding the primary end point at 9 months there was no difference in clinical outcomes between the two treatment regimens. Similarly, there was no significant difference in ischemic outcomes or TIMI major bleeding. Any bleeding defined by the Bleeding Academic Research Consortium (BARC) criteria occurred in 40% of patients at 9 months with longer triple therapy, which is in line with the WOEST study, and in 38% of patients treated for 6

weeks. This difference was not statistically significant. A post hoc landmark analysis, one that assessed any BARC bleeding from 6 weeks to 9 months, found that there was a reduction in BARC bleeding in patients who received triple therapy for the shorter duration. The results are different from those of the WOEST trial, where there was a significant reduction in any bleeding complications and a decrease in ischemic complications with dual therapy. Even more perplexing is the fact that there seemed to be no effect on bleeding outcomes between the 6-week and 9-month treatment strategies.

NEWER ANTIPLATELET AGENTS IN TRIPLE THERAPY

It is obvious that most observations regarding triple therapy are only applicable to the combination of aspirin/clopidogrel/warfarin. One may presume that the substitution of more potent antiplatelet agents, such as prasugrel or ticagrelor for clopidogrel, would further increase the risk of bleeding. Both agents demonstrated a significant reduction in the rate of death, MI, and stroke when compared with clopidogrel.^{35,36} However, the main drawback of these third generation P2Y12 inhibitors is an observed increased incidence of major bleeding compared to clopidogrel, conceivably further limiting their use in triple therapy.^{35,37} Data regarding ticagrelor as part of triple therapy are not available. As for prasugrel, a recent prospective observational study,³⁸ evaluating the role of prasugrel as part of triple therapy, suggested that prasugrel, compared to clopidogrel, as part of triple therapy in patients on chronic OAC, is associated with nearly 5-fold greater TIMI major bleeding than clopidogrel therapy, without differences regarding composite ischemic endpoints between both groups. High on treatment platelet reactivity, determined by impedance aggregometry, was the indication for prasugrel in the majority of patients (86%). This study was not randomized, resulting in significant imbalances in baseline characteristics, with higher-risk profiles in prasugrel users, and a very low number of patients receiving prasugrel (prasugrel n=21 vs clopidogrel n=356). However, these findings do correspond with earlier observations that prasugrel has higher bleeding rates when compared with clopidogrel.³⁶ Thus, triple therapy with the newer generation of P2Y12 inhibitors seems to be even more hazardous than that with clopidogrel and should therefore be avoided, if at all possible, until clinical data are available.

RESISTANCE TO CLOPIDOGREL

Of significant clinical importance is the phenomenon of antiplatelet resistance and associated high on-treatment platelet reactivity (HPR). Despite well-documented efficacy, recurrent thrombotic event occurrence, particularly stent

thrombosis, have been repeatedly demonstrated in stented patients treated with aspirin and clopidogrel. The latter observation stimulated the close scrutiny of the pharmacodynamic effects of clopidogrel and revealed the ‘wide variability’ and the phenomenon of ‘antiplatelet resistance’.^{39,40} Generally, a one size fits all nonselective strategy is used without an assessment of pharmacodynamic efficacy of clopidogrel therapy. However, pharmacodynamic studies revealed various limitations of clopidogrel metabolism and numerous factors, such as genetic and drug-drug interactions, influence the antiplatelet response to clopidogrel therapy. Recent studies have highlighted the relation of single nucleotide polymorphisms of genes involved in clopidogrel absorption and metabolism to reduced pharmacokinetic and pharmacodynamic responses to clopidogrel. In the absence of any drug interactions, 12% to 15% of the inter-individual variability to the drug is accounted for by polymorphic variations in the gene for cytochrome P450 2C19. Patients who have a poor inhibitory effect of clopidogrel and/or carry 1 or more loss-of-function alleles for cytochrome P450 2C19 have high on-treatment platelet reactivity and are at higher risk of thrombotic events, whereas those with a large inhibitory effect of clopidogrel have low on-treatment platelet reactivity and appear to hold a higher risk of bleeding.^{41,42} Common polymorphisms in the CYP2C19 gene, seen in approximately 30% of whites, 40% of blacks, and >55% of East Asians, significantly diminish both the pharmacokinetic and pharmacodynamic responses to clopidogrel by approximately one quarter to one third. However, clopidogrel is pharmacodynamically effective in about two thirds of patients undergoing PCI; these patients do not have HPR.⁴³

High on-treatment platelet reactivity to ADP (HPR) during clopidogrel therapy is an independent risk factor for both acute as well as long-term ischemic event occurrence in post-PCI patients, including stent thrombosis, while recent observational studies demonstrated a link between low on-treatment platelet reactivity to bleeding.^{43,44} This potentially complicates the interpretation of data related to dual therapy with clopidogrel and VKA, because levels of platelet reactivity may vary widely among patients. For example, patients with a poor response to clopidogrel who develop a low INR may be at higher risk of stent thrombosis and other thrombotic events, whereas patients with a large inhibitory effect of clopidogrel who develop a high INR may be at higher risk of bleeding. In addition, there is a possibility that VKA itself might modify clopidogrel drug responsiveness and efficacy. Both clopidogrel and VKA are metabolized by the hepatic cytochrome P450 system. Concomitant phenprocoumon use has been shown to significantly attenuate the antiplatelet effects of clopidogrel and has been associated with a significantly higher level of HPR.⁴⁵ While HPR has been linked with a poor outcome, it is still unknown if the association between HPR and thrombotic events is as strong in patients concomitantly treated with coumadin derivatives as in patients who do not receive these drugs. Furthermore, currently there

is no evidence for tailoring antiplatelet therapy based on the presence of HPR.³⁹ Although switching from clopidogrel to the stronger antiplatelet agents prasugrel or ticagrelor might be an option in HPR patients without VKA, it is even more unclear what the optimal treatment strategy could be for HPR patients with VKA, given the heightened bleeding risk with these agents compared to clopidogrel.³⁵⁻³⁸

DUAL ANTIPLATELET THERAPY DURATION

The optimal duration of dual antiplatelet therapy, which clearly influences the duration of triple therapy, remains to be determined. In the Dual Antiplatelet Therapy (DAPT) Study,⁴⁶ 30 vs 12 months of dual antiplatelet therapy were associated with reduced rates of stent thrombosis (0.4% vs 1.4%; hazard ratio, 0.29 [95% CI, 0.17 to 0.48]; $P < 0.001$) and MACCE (4.3% vs 5.9%; hazard ratio, 0.71 [95% CI, 0.59 to 0.85]; $P < 0.001$). The rate of MI was lower with prolonged thienopyridine treatment than with placebo (2.1% vs 4.1%; hazard ratio, 0.47; $P < 0.001$). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (hazard ratio, 1.36 [95% CI, 1.00 to 1.85]; $P = 0.05$); a rather unexpected finding, mostly driven by an increase in non-cardiovascular deaths. The rate of moderate or severe bleeding was also increased with continued thienopyridine treatment (2.5% vs 1.6%, $P = 0.001$). An elevated risk of stent thrombosis and MI was observed in both groups during the 3 months after discontinuation of thienopyridine treatment. A meta-analysis, involving 14 randomized controlled trials, including the DAPT Study, that randomly assigned 69 644 participants to different durations of dual antiplatelet therapy was recently published.⁴⁷ Compared with aspirin alone or short duration dual antiplatelet therapy (≤ 6 months), continued treatment was not associated with a difference in all-cause mortality (hazard ratio 1.05, 95% CI 0.96–1.19; $p = 0.33$). Similarly, cardiovascular (1.01, 0.93–1.12; $p = 0.81$) and non-cardiovascular mortality (1.04, 0.90–1.26; $p = 0.66$) were no different with extended duration versus short duration dual antiplatelet therapy or aspirin alone.

Of significant importance is the evolution in stent technology. A network meta-analysis looking at several trials involving approximately 100 000 patients, revealed that newer generation stents are associated with a lower rate of stent thrombosis and probably a lower event rate,⁴⁸ while recent data suggest that 6 or even 3 months of DAPT might be long enough,⁴⁹⁻⁵⁵ instead of the standard 12 months.^{3,4,56} A number of trials are ongoing. The expectation is that the duration of dual antiplatelet therapy will become shorter, and, therefore, the exposure to triple therapy will be less. How this will play out in our approach to dual and triple antithrombotic therapy in the next few years remains to be seen.

NOACS IN TRIPLE THERAPY

New oral anticoagulants (NOACs), e.g., dabigatran, rivaroxaban, apixaban and edoxaban have recently emerged. The potential role of NOACs or optimal NOAC regimen for patients with ACS or PCI with stenting and AF has not been directly assessed in randomized controlled trials. The safety of these drugs on top of antiplatelet therapy has been questioned in large trials of patients presenting with ACS. In this setting, NOACs on top of single or dual antiplatelet therapy demonstrated a constant increase in bleeding events, while the efficacy of this combination remained in most studies unclear. For example, the addition of apixaban, a factor Xa inhibitor, at a dose shown to be more effective than warfarin in stroke prophylaxis in AF, to aspirin plus clopidogrel, was associated with excessive bleeding that resulted in the premature termination of a major ACS trial.⁵⁷ Greater bleeding was also observed with AF-effective doses of dabigatran in addition to aspirin plus clopidogrel versus aspirin plus clopidogrel.⁵⁸ One notable exception, is the investigational use of rivaroxaban in a reduced twice-daily dose (reduced as compared with the dose approved for nonvalvular AF thromboprophylaxis), in conjunction with DAPT, post-ACS. In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction (ATLAS ACS 2–TIMI 51) study,⁵⁹ rivaroxaban 2.5 mg twice daily significantly reduced the occurrence of the primary efficacy end point (death from cardiovascular causes, MI, or stroke), cardiovascular mortality and all-cause mortality as compared with placebo with a modest increase in major bleeding but no increase in fatal bleeding.

More data on the effects of concomitant prescription of NOACs and antiplatelet drugs derived from post hoc analyses of randomized controlled trials of NOACs in non-valvular AF patients,⁶⁰ as well as “real-life” nationwide AF patient data.^{61–63} A recent meta-analysis included 7 published randomized, placebo-controlled phase II and III studies of NOACs in ACS.⁶⁴ The database consisted of 30 866 pts, 4135 (13.4%) on single, and 26 731 (86.6%) on dual antiplatelet therapy, with a non-ST- or ST-elevation ACS within the last 7–14 days. Major adverse cardiovascular events (MACEs) were defined as the composite of all-cause mortality, MI, or stroke; and clinically significant bleeding as the composite of major and non-major bleeding requiring medical attention according to the study definitions. When compared with aspirin alone the combination of an oral anticoagulant and aspirin reduced the incidence of MACE [hazard ratio (HR) and 95% confidence interval 0.70; 0.59–0.84], but increased clinically significant bleeding (HR: 1.79; 1.54–2.09). Compared with dual antiplatelet therapy with aspirin and clopidogrel, adding an oral anticoagulant decreased the incidence of MACE modestly (HR: 0.87; 0.80–0.95), but more than doubled the bleeding (HR: 2.34; 2.06–2.66).

In general, in the setting of ACS, triple therapy with dual antiplatelet therapy and NOACs is associated with at least a doubling of the risk of major bleeding,⁶⁵ as similarly reported for VKAs in the WOEST trial²³ and consistent with the nationwide registry data from Denmark.²⁸ Even though there are no head-to-head comparisons yet available of triple therapy with traditional VKA and triple therapy with the NOACs, there is no strong evidence to suggest that NOACs behave differently to VKAs in the setting of ACS or stenting. Furthermore, there is a paucity of data on the use of the NOACs in combination with dual antiplatelet therapy with aspirin and the new P2Y12 inhibitors, prasugrel or ticagrelor. Limited data suggest that use of the new P2Y12 inhibitors would increase the risk of major bleeding, and thus, clopidogrel would be the preferred P2Y12 inhibitor. Further studies evaluating NOACs in combination with effective single or dual antiplatelet therapy and the optimal duration of triple antithrombotic therapy are warranted.

CURRENT GUIDELINES

The management of patients on OAC undergoing PCI with stenting remains controversial. Nonetheless, some guidance for the everyday management of this patient subset has been developed by panels of experts, and official scientific bodies.^{6–8,66,67} The European Society of Cardiology (ESC) guidelines recommend triple therapy with aspirin, clopidogrel, and VKA in patients with an indication for therapeutic anticoagulation and ACS and/or coronary stent implantation.⁶ The recommended duration of triple therapy ranges from 2–4 weeks through 6 months depending on the individual risk of thromboembolism (as assessed by the CHA₂DS₂-VASc score), and bleeding (as assessed by the HAS-BLED score), as well as the clinical context in which PCI with stenting is performed (elective vs ACS), and the type of stent implanted (DES vs BMS). Triple therapy is recommended for the duration of 1 month after BMS implantation and should be prolonged up to 6 months in the case of implantation of a DES. In the case of ACS, triple therapy should be also prolonged to 6 months irrespective of the stent type implanted. To reduce bleeding complications, the INR should be maintained at a lower target range of 2–2.5 instead of 2–3. Aspirin and clopidogrel are given in the usual doses as recommended for stent implantation (≤100 mg/day and 75 mg/day respectively). The 2012 American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy for AF gave similar recommendations also using aspirin, clopidogrel, and VKA as antithrombotic drugs.^{66,67} The duration of triple therapy ranges from 1 month (BMS) to 3–6 months (DES) depending on the stent type. Both guidelines agree that after 1 year, anti-platelet therapy can be stopped and VKA continued as a single long-term prevention of thromboembolism in AF.

In August 2014 comprehensive consensus recommendations were issued by the ESC Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI), and Acute Cardiovascular Care Association (ACCA), endorsed by the Heart Rhythm Society (HRS), and Asia-Pacific Heart Rhythm Society.⁶⁸ The major “breakthrough” of this paper, in comparison with previous consensus documents, is the suggestion that NOACs can be used in the triple therapy regimen in combination with clopidogrel and low-dose aspirin with the same treatment strategies as VKAs. Where a NOAC is used in combination with clopidogrel and/or low-dose aspirin, the lower tested dose for stroke prevention in AF (that is, dabigatran 110 mg bid, rivaroxaban 15 mg od or apixaban 2.5 mg bid) may be considered. When VKAs are used as part of triple therapy, attention should be given to high quality OAC (the time in the therapeutic range should be >70%) while frequent INR monitoring (every two weeks) with the INR targeted at 2.0–2.5 and routine gastric protection with proton pump inhibitors (PPIs) for all patients, are among measures to minimize bleeding complications. New generation DES are generally preferable over BMS, particularly in patients at low bleeding risk (HAS-BLED 0–2). Upon completion of the triple therapy course, one antiplatelet agent (either aspirin or clopidogrel, depending on the individual risk of bleeding, especially gastrointestinal and stent thrombosis) should be discontinued, and combination of OAC, and single antiplatelet agent continued up to one year. Following the first 12 months from PCI with stenting and/or ACS, the risk of stent thrombosis and/or recurrent cardiac events, is diminished, so that ongoing single antiplatelet agent (either aspirin or clopidogrel) should be discontinued, and OAC monotherapy, with either VKA (target INR 2-3) or NOAC (standard dosing, unless other indications for reduced dose are present), continued indefinitely (Table 1).

In the recently published American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guidelines for the Management of Patients With Atrial Fibrillation it is stated that after coronary revascularization (percutaneous or surgical) in patients with AF and a CHA₂DS₂-VASC score ≥ 2 , it may be reasonable to use clopidogrel concurrently with oral anticoagulants but without aspirin (class IIa, level of evidence B).⁶⁹

The recommendations are largely based upon expert opinion, rather than strong registry and randomized trial data and represent level of evidence C. Therefore, the ultimate judgment regarding care of a particular patient should be made by the healthcare provider and the patient himself, in light of all of the circumstances presented by that patient. There is a need to balance stroke prevention against stent thrombosis following PCI vs the harm of bleeding with combination antithrombotic therapy.

ONGOING TRIALS

The optimization of antithrombotic treatment for patients on chronic OAC is still ongoing. More and more attention is given to this clinical dilemma. Currently, some randomized controlled trials are ongoing regarding the optimal antithrombotic treatment in patients on chronic OAC undergoing PCI with stent implantation. The Anticoagulation in Stent Intervention trial, MUSICA-2,⁷⁰ is a randomized controlled trial that will compare DAPT with triple therapy in patients with AF and low-moderate risk of stroke (CHADS₂<2) undergoing PCI with stent implantation. Endpoints of MUSICA-2 are death, stroke, MI, embolization, and stent thrombosis at 12 months. The PIONEER AF-PCI study⁷¹ is a phase III clinical study of rivaroxaban, investigating the optimal antithrombotic treatment in patients with nonvalvular AF undergoing PCI with stent implantation. The PIONEER AF-PCI study will enroll approximately 2,100 patients worldwide. The trial will assess the safety of two rivaroxaban treatment strategies and a dose-adjusted VKA treatment strategy during 12 months of therapy. Primary endpoint is the composite of TIMI major bleeding, TIMI minor bleeding, and bleeding requiring medical attention. The RE-DUAL PCI (Randomized Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy Strategy with Warfarin in Patients with non valvular AF that have undergone PCI with Stenting) trial was also started recently.⁷² In this trial, the safety and efficacy of 2 dabigatran treatment strategies will be tested versus dose-adjusted VKA treatment. Unfortunately, the superior arm of the WOEST trial (VKA and clopidogrel) was left out of both trials. The results of these ongoing trials will provide more evidence which will further aid in optimizing treatment for patients on chronic anticoagulation undergoing PCI with stent implantation.

CONCLUSION

There is no optimal antithrombotic treatment available for patients on chronic OAC undergoing PCI with stent implantation. The three risks to be considered in selecting antithrombotic therapy are: stroke/thromboembolism, stent thrombosis and major bleeding. Based on weak evidence, guidelines recommend triple therapy by OAC, aspirin, and clopidogrel. However, several trials have shown that the reduction of thromboembolic events by triple therapy is offset by an increase in bleeding complications. As bleeding complications are associated with increased mortality, the effectiveness of this treatment strategy is strongly doubted. Newly developed oral anticoagulants and stronger antiplatelet drugs are associated with increased bleeding, making triple therapy even more hazardous. With the aging population and increasing prevalence of AF, the relevance of this clinical dilemma is

further increasing. A number of recent observations have lent insight into optimizing the balance of safety and efficacy for those patients deemed appropriate for triple therapy. The WOEST trial delivered a promising new treatment strategy of combining clopidogrel and OAC and thus omitting aspirin. Treatment by OAC and clopidogrel proved to reduce bleeding risk without an increase in thromboembolic events. This reduction in bleeding risk has been confirmed by a large Danish registry. These findings can be seen as a breakthrough in the treatment of patients on chronic OAC undergoing PCI with stent implantation, bringing us closer to the optimal antithrombotic treatment of these patients. Dual therapy with oral anticoagulants and clopidogrel may be considered as an alternative to triple therapy in selected AF patients at low risk of stent thrombosis/recurrent cardiac events. However, these findings still need to be confirmed in larger studies. There are ongoing trials which will provide evidence that will further aid in optimizing treatment for patients on chronic anticoagulation undergoing PCI with stent implantation. Balancing the intensity of anticoagulant and antiplatelet therapy is a delicate act and accurate stratification of thromboembolic and bleeding risk on an individual basis is warranted.

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REMOVING ASPIRIN FROM TRIPLE ANTITHROMBOTIC THERAPY

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