THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Triple Therapy for Atrial Fibrillation and Percutaneous Coronary Intervention
A Contemporary Review

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ABSTRACT

Chronic oral anticoagulant therapy is recommended (class I) in patients with mechanical heart valves and in patients with atrial fibrillation with a CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category) score ≥1. When these patients undergo percutaneous coronary intervention with stenting, treatment with aspirin and a $P2Y_{12}$ receptor inhibitor also becomes indicated. Before 2014, guidelines recommended the use of triple therapy (vitamin K antagonists, aspirin, and clopidogrel) for these patients. However, major bleeding is increasingly recognized as the Achilles' heel of the triple therapy regimen. Lately, various studies have investigated this topic, including a prospective randomized trial, and the evidence for adding aspirin to the regimen of vitamin K antagonists and clopidogrel seems to be weakened. In this group of patients, the challenge is finding the optimal equilibrium to prevent thromboembolic events, such as stent thrombosis and thromboembolic stroke, without increasing bleeding risk. (J Am Coll Cardiol 2014;64:1270–80) © 2014 by the American College of Cardiology Foundation.

Chronic oral anticoagulation (OAC) is necessary in patients with mechanical heart valves and in patients with atrial fibrillation (AF) and a CHA_2DS_2VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke or transient ischemic attack or thromboembolism, Vascular disease, Age 65 to 74 years, Sex category) score ≥1 (1,2). About 30% of these patients have concomitant coronary artery disease (CAD). When these patients have to undergo percutaneous coronary intervention (PCI), additional dual antiplatelet therapy (DAPT) with aspirin and clopidogrel becomes indicated to prevent stent thrombosis (3–5).

In a rapidly aging population, the number of patients experiencing both AF and CAD is steadily increasing. However, triple therapy produces a high annual bleeding risk of up to 45%, and an association has been seen among major bleeding events, blood transfusion, and increased mortality risk (6–11). Triple therapy, including vitamin K antagonists (VKAs), aspirin, and clopidogrel (for as short a time as

possible), was recommend by the 2010 European guidelines, whereas the recent 2014 North American Guidelines recommend the combination of VKA and clopidogrel with a Class IIb, Level of Evidence: B recommendation (4,12). The 2010 European guidelines were based on expert opinion and not on randomized trials (4). Recently, new evidence has emerged suggesting that the increased bleeding risk outweighs the efficacy (preventing stent thrombosis, myocardial infarction [MI], stroke, and thromboembolism) benefit of triple therapy in these patients, and possibly, a new strategy of VKA and a $P2Y_{12}$ inhibitor alone could be preferred (6,12-15). This review will summarize guidelines, focus on some key evidence from the last several years, and address unanswered questions.

GUIDELINES

European guidelines recommend triple antithrombotic therapy in a patient with AF undergoing PCI (4). This triple therapy consists of VKA with a revised target for international normalized ratio (INR) 2.0 to 2.5, aspirin, and clopidogrel. Aspirin has always been the cornerstone in treating patients with acute coronary syndrome (ACS) and/or PCI, VKAs are needed for stroke prevention, and a $P2Y_{12}$ inhibitor is essential for the prevention of stent thrombosis (16-19). However, this triple therapy strategy has never been studied prospectively until the recent WOEST (What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing) trial (6).

European guidelines recommend continuing VKAs and giving triple therapy for as short a period as possible after PCI, in general until stent strut endothelialization is expected to be complete. The duration of prescribed triple therapy mostly depends on bleeding risk and stent type, and various recommendations are made to limit bleeding risk, as mentioned below.

Recently, following the results of the WOEST trial, the American Heart Association/American College of Cardiology/Heart Rhythm Society issued a Class IIb (Level of Evidence: B) recommendation for the combination of VKA and clopidogrel after PCI in patients with AF (12).

NEW EVIDENCE

In the randomized, controlled WOEST trial, 573 patients using VKA undergoing PCI in an open-label, intention-to-treat design were randomized to either double therapy (VKA and clopidogrel) or triple therapy (VKA, clopidogrel, and aspirin) (6,20). The primary endpoint was the occurrence of any bleeding event. At 1 year, the cumulative incidence of all Thrombolysis In Myocardial Infarction (TIMI) bleeding events was 19.4% in the dual-therapy group compared with 44.4% in patients treated with triple therapy (hazard ratio [HR]: 0.36; 95% confidence interval [CI]: 0.26 to 0.50; p < 0.0001) (6,21). The 1-year incidence of serious bleeding according to Bleeding Academic Research Consortium (BARC) criteria 3 also was significantly lower in the dual therapy arm (6.5% vs. 12.7%; HR: 0.49; 95% CI: 0.28 to 0.86; p = 0.011) (6,22). Furthermore, dual therapy produced a significantly lower rate of blood transfusions than did triple therapy (3.9% vs. 9.5%; odds ratio [OR]: 0.39; 95% CI: 0.17 to 0.84; p = 0.011). Secondary endpoints included major adverse cardiac and cerebrovascular events (MACCE) defined as the composite of death, MI, stroke, systemic embolism, target vessel revascularization (TVR), and stent thrombosis, which occurred in 11.1% of patients receiving dual therapy compared with 17.6% of patients receiving triple therapy (HR: 0.60; 95% CI: 0.38 to 0.94; p = 0.025). The WOEST trial indicates that double therapy (VKA and clopidogrel without aspirin) significantly reduces bleeding complications as compared with triple therapy after PCI in patients with an indication for OAC. Dropping aspirin in this high-risk group led to a more than 50% reduction in the occurrence of bleeding complications.

After the WOEST trial results were published, expert opinion was that it was too early to change the guidelines, even though current recommendations are not based on randomized trials (23). The reasons given for the reluctance to change guidelines were based on the limitations of the WOEST trial. First, the number of patients randomized was relatively low (n = 573) and not every patient had AF (approximately 70%). Second, there was no significant difference in TIMI major bleeding, and the absolute number of major bleeds was rather low (16 vs. 9). The difference in bleeding was mainly driven by TIMI minor bleeding. However, when bleeding events were classified according to the new standardized BARC bleeding criteria, there was a significant difference in BARC 3 bleeding, which corresponds with major bleeding, in favor of the combination of clopidogrel and VKA (6,22). Additionally, the authors emphasized the importance of minor bleeding, because these events can lead to cessation of medication (e.g., clopidogrel) and major adverse events such as stent thrombosis (6). Third, compared with current recommendations, the rate of proton pump

inhibitor (PPI) use at baseline was low (37%), the radial approach was used infrequently (26%), bare-metal stents (BMS) were used in a minority of patients (31%), periprocedural target INR was 2.0, and the long-term target INR was not lowered post-procedurally (target INR 2 to 3 for AF). These results are compared with current guidelines, which recommend standard PPI use, radial approach, BMS use, and a lower long-term target INR of 2 to 2.5 in this patient population. The conflict with the guidelines is easily explained: in 2008, when the WOEST study was designed, these recommendations were not available yet (4,12). Fourth, the number of deaths was significantly higher with triple therapy, but this was driven by a higher number of noncardiac deaths, which might be due to a play of chance. Fifth, there was no information on the time of INR in the therapeutic range. However, we know from the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial that the quality of oral anticoagulation is good in the Netherlands and Belgium, with a therapeutic range of 65% for patients treated in Belgium and up to 70% in the Netherlands (24). Finally, the study was not powered to show noninferiority of the secondary outcomes and the number of patients at high risk of stent thrombosis, such as those with recent ACS, was limited to a quarter of the WOEST trial participants. The study population was heterogeneous, because the goal was to conduct a trial with a real-life population representing daily practice (6). Moreover, the WOEST trial was the first to break the taboo of omitting treatment with aspirin after PCI, hypothesizing that inhibition of thrombin (a strong platelet activator) with VKA and inhibition of the $P2Y_{12}$ receptor with clopidogrel would make inhibition of cyclo-oxygenase-1 less important in the protection against thrombotic and thromboembolic events, particularly since the $P2Y_{12}$ receptor plays a major role in amplifying the effects of thromboxane A_2.

Recently, a Danish group published results of a real-life nationwide retrospective registry of 12,165 patients that supported the findings in the WOEST trial (13). The authors investigated the risk for thrombosis and bleeding according to multiple antithrombotic regimens after MI or PCI in AF patients. After 1 year, there was no increased risk of recurrent coronary events for dual therapy (HR: 0.69; 95% CI: 0.48 to 1.00) relative to triple therapy, and bleeding risk was also nonsignificantly lower for VKA plus clopidogrel (HR: 0.78, 95% CI: 0.55 to 1.12). Moreover, there was a similar risk for all-cause mortality in patients treated with VKA plus clopidogrel as well as those receiving triple therapy, but the combinations of VKA plus aspirin and aspirin plus clopidogrel were associated with a significant increase in all-cause mortality compared with triple therapy (13).

The most important aspect of the Danish registry: it suggests that the combination of OAC plus clopidogrel is sufficient to reduce the risk of thrombotic events. This was the missing part of the puzzle, since the WOEST trial was not powered to show non-inferiority on the secondary composite MACCE end-point. Also, the Danish registry is now the second study in which no beneficial effect of adding aspirin to VKA and clopidogrel was found in this high-risk patient group. The authors explain that the bleeding rate was lower in the VKA plus clopidogrel patient group, but this difference did not reach statistical significance, likely because this registry only included bleeding events serious enough to warrant hospitalization, whereas all bleeding events were collected in the WOEST trial.

Two other registries that confirmed the efficacy and safety of VKA plus clopidogrel in patients with AF who underwent PCI were recently published. In the AFCAS (Atrial Fibrillation Undergoing Coronary Stenting) trial, a prospective nonrandomized study including 975 patients, the 1-year efficacy and safety of triple therapy, DAPT, and VKA plus clopidogrel was comparable (15). A total of 221 patients who received drug-eluting stenting (DES) were included in another German registry with a mean follow-up of 19 months. Despite a shorter period of clopidogrel therapy (6 to 12 months) followed by VKA monotherapy, the combination of OAC plus clopidogrel again appeared both safe and effective at long-term follow-up (14).

CLINICAL IMPORTANCE AND PREVENTION OF BLEEDING AFTER PCI

Major bleeding events and blood transfusions have been associated with increased risk of death in several studies (7,8,25-28). This has led to an increased awareness of this problem, and predictors of bleeding events in PCI patients have been identified. Strong predictors we can influence are the choice of vascular access (radial vs. femoral) and the choice of antithrombotic regimen (28-31).

The importance of bleeding as an adverse event is underscored by the fact that bleeding has now become a primary endpoint in many PCI trials (7,17,28,32,33). In an effort to standardize the definition and detection of bleeding events in different studies, the Academic Research Consortium published and validated new bleeding criteria (BARC) (22,34). Before the BARC criteria were established, different trials used different bleeding definitions, which was an important hindrance when trying to

compare bleeding rates across trials (21,35). A second obstacle when assessing bleeding rates is the possible under-reporting of bleeding events in studies (36). Therefore, the impact of bleeding could be even larger in real life than reported in these studies. This could also explain why the bleeding rate reported in the WOEST trial stood very high compared to other trials, as this study was specifically designed to detect bleeding events and data were collected for all types of bleeding rather than solely focusing on major bleeding events (6).

Another issue that needs to be addressed: patients with AF in need of PCI represent a population that mainly consists of older patients with high rates of comorbidity. Many are octogenarians, a group frequently excluded from or under-represented in randomized clinical trials. It is questionable whether our current guidelines can be applied to this group. Additionally, we know that older patients with AF have a higher CHA_2DS_2-VASc score as well as a higher bleeding risk when treated with VKAs (37). In this population, the role of nonmajor bleeding should not be underestimated. Even superficial or "nuisance" bleeding can lead to discontinuation of antiplatelet therapy, which can lead to subsequent thrombotic complications, such as stent thrombosis. Clearly, this high-risk population, often with multiple comorbidities, is more prone to experience treatment-related adverse events (4,38).

Over the last years, numerous risk factors have been associated with higher bleeding risk: age >55 years, female sex, glomerular filtration rate <60 ml/min, pre-existing anemia, use of low-molecular-weight heparin (LMWH) <48 h before PCI, use of glycoprotein IIb/IIIa inhibitors, and the use of an intra-aortic balloon pump (27,39,40).

To estimate bleeding risk, many bleeding risk-prediction scores have been proposed, and the best known is the HAS-BLED score (41). The HAS BLED score estimates the risk for major bleeding for patients on anticoagulation and is based on the presence of some high-risk features as hypertension, stroke, renal disease, liver disease, prior major bleeding, age older than 65 years, labile INR, the use of medication predisposing to bleeding and weekly alcohol usage. Shown to be useful in the assessment of bleeding risk, the HAS-BLED score also demonstrates some predictive value for cardiovascular events and mortality in anticoagulated patients with AF. The data are consistent with the relationship between thrombosis and bleeding and confirm that the number of bleeding and thrombotic events is higher in patients with high comorbidity at baseline (42). The higher the patient's bleeding risk, the more measures should be taken to avoid and prevent bleeding, such as the standardized use of a risk score assessment tool, a radial approach, smaller sheath size and early removal, BMS use, routine use of PPI, utilization of a target INR range of 2.0 to 2.5, the choice and dose of antithrombotics and $P2Y_{12}$ inhibitors, and avoidance of all of the following: crossing over from 1 antithrombotic to another, an intra-aortic balloon pump, use of glycoprotein IIb/IIIa inhibitors, and periprocedural bridging with LMWH if not strictly indicated (4,12,28).

PERIPROCEDURAL MANAGEMENT

Besides the choice between dual or triple therapy, another decision looms for patients on OAC who have a planned PCI: what to do with the VKA in the periprocedural period? In patients on a VKA scheduled for PCI, the VKA is often discontinued several days prior to intervention, exposing the patient to a higher risk of thromboembolic complications. Occasionally, the periods before and after the intervention are bridged (until a therapeutic INR is reached) with additional unfractionated heparin or LMWH, exposing the patient to excess bleeding risk. When patients are treated with 4 blood thinners (OAC, clopidogrel, aspirin, and heparin) for a short period after the intervention until a therapeutic INR is reached, the bleeding risk is particularly high (43). Additionally, reinitiation of VKA may cause a transient prothrombotic state due to protein C and S suppression (4). Bridging also prolongs hospitalization, which is unnecessary and wasteful from an economic point of view.

Recent European guidelines recommended uninterrupted VKA as the preferred strategy in patients with AF undergoing PCI (4). In the AFCAS trial and in a recent subanalysis of the WOEST trial, uninterrupted OAC was not associated with an increased risk of bleeding or thromboembolic events compared with bridging therapy (43,44). Furthermore, bleeding and other adverse events were not associated with INR levels in these studies (43,44). Additional support comes from the BAAS (Prospective Balloon Angioplasty and Anticoagulation) study, where the combination of aspirin plus VKA compared with aspirin alone was safe and effective during PCI performed with a target INR of 2.1 to 4.8 (45). So, the strategy of uninterrupted VKA not only leads to cost savings, but it is also as safe as bridging and, therefore, may be the preferred strategy.

Similarly, the radial approach offers the better strategy in these patients based on proven lower rates of bleeding and a possible reduction in mortality, especially in ST-segment elevation myocardial infarction patients (30). One question regarding the

periprocedural strategy remains unanswered. Like coronary angiography, it might be an option to perform PCI without administration of additional heparin in patients on therapeutic anticoagulation with a VKA (46). However, physicians did not avoid an additional heparin bolus during PCI in most patients included in the WOEST trial. This strategy was probably chosen due to fear of periprocedural thromboembolic complications such as stent thrombosis (43). On the one hand, this additional heparin bolus could explain the higher-than-expected bleeding rates in the original WOEST trial (6). In the AFCAS study, 48% of patients also received a preprocedural bolus of heparin or LMWH in addition to therapeutic anticoagulation in the uninterrupted VKA group (44). On the other hand, a recently published study showed that the incidence of radial artery occlusion in patients receiving VKA who undergo transradial coronary angiography is higher in patients who do not receive an additional standard intravenous unfractionated heparin bolus (47). As of yet, there is insufficient evidence to determine if a heparin bolus is necessary in patients with therapeutic INR requiring PCI. Furthermore, it is unclear what the optimal dosage would be if a heparin bolus is indeed necessary.

POSSIBLE PITFALLS AND OTHER UNANSWERED QUESTIONS

In patients treated with triple therapy, bleeding occurs frequently in the gastrointestinal tract, making protection of the gastric mucosa reasonable. Yet, some papers have suggested that there is a potential danger in combining omeprazole and clopidogrel due to impairment in the formation of the active metabolite of clopidogrel by omeprazole, leading to diminished antiplatelet effect (48,49). However, no clinical consequences of this interaction have been demonstrated so far. The single randomized controlled trial on this topic, COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial), showed that in patients post-ACS, the combination of omeprazole 20 mg and clopidogrel 75 mg was superior to the combination of clopidogrel and placebo in reducing the rate of gastrointestinal bleeding, with no significant difference in the rate of adverse cardiovascular events (50). Subsequent reports have suggested that PPI use should not be avoided but rather encouraged in patients on multiple antiplatelet medications (49,51).

A second possible pitfall for clopidogrel is the wide interindividual variability to the drug, even in the absence of any drug interactions, with 12% to 15% of the variability accounted for by polymorphic variations in the gene for cytochrome P450 2C19 (52-54). Patients who have a poor inhibitory effect of clopidogrel and/or carry 1 or more loss-of-function alleles for cytochrome P450 2C19 are at higher risk of stent thrombosis, whereas those with a large inhibitory effect of clopidogrel appear to hold a higher risk of bleeding. This potentially complicates the interpretation of data related to dual antiplatelet therapy with clopidogrel and VKA, because levels of platelet reactivity may vary widely between 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 (52-54).

A third conceivable pitfall is the 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 high on-platelet reactivity (HPR) (55). 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 coumarin derivates as in patients who do not receive these drugs. Furthermore, there currently is no evidence for tailoring antiplatelet therapy based on the presence of HPR (53). 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 (53). Theoretically, ticagrelor and prasugrel could be good alternatives for clopidogrel as they provide more potent platelet inhibition with less interindividual variability (56,57). However, bleeding risk also increases with treatment with ticagrelor and prasugrel as compared with clopidogrel (56,57).

The fourth and very important question to tackle: why would we want to replace the combination of DAPT plus VKA with the combination of VKA plus clopidogrel? Since 2001, DAPT has been standard therapy after PCI. The CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study included 12,562 patients who had presented within 24 h after ACS without ST-segment elevation and were randomized to receive either clopidogrel or placebo in addition to aspirin. Clopidogrel had beneficial effects because of a significant reduction in MACCE (9.3% vs.

11.4%; p < 0.001) (58). So then, why would we try to replace aspirin with VKA? In these patients who also need VKA for stroke prevention, there are many possible therapeutic combinations, but it has already been shown that the combination of VKA plus aspirin (leaving out clopidogrel) led to an increased rate of MI and stent thrombosis (13,18). In the ACTIVE W (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) study, withholding VKA (thus treating patients only with aspirin and clopidogrel) in patients with AF led to an increased rate of cardiovascular events and mortality (16). This leaves triple therapy and the combination of VKA and clopidogrel as the only alternatives.

But then, why drop aspirin? The hypothesis of the WOEST trial was that thrombin inhibition with VKA and inhibition of $P2Y_{12}$ with clopidogrel would lessen the importance of cyclo-oxygenase-1 inhibition by aspirin for protection against thrombotic and thromboembolic events, whereas triple therapy has been associated with an increased risk of both fatal and nonfatal bleeding (6,7,59,60). This hypothesis was based on the results of 2 large randomized trials that compared VKA with aspirin in the prevention of reinfarction and stroke in patients who had experienced an MI. Vitamin K antagonist treatment was associated with lower recurrence rates but higher risks of bleeding in these studies (61,62). Therefore, VKA seems at least as good as aspirin in protecting patients from thrombotic events. The hypothesis that aspirin is not needed in VKA-treated patients who undergo PCI with stent implantation is supported by the results of the WOEST trial. Nevertheless, the WOEST trial was not powered to detect differences in the occurrence of thrombotic events, such as stent thrombosis, when aspirin was omitted, and this would need to be studied in a larger trial. Meanwhile, these results were confirmed by a large Danish national registry, the AFCAS trial, and a smaller German trial all showing favorable results for the combination of VKA and clopidogrel (6,13-15) (**Central Illustration**).

The fifth dilemma focuses on how to overcome the possibility of unopposed thromboxane-dependent platelet activation after stopping aspirin with subsequent cardiovascular events (63). In 2 patient series in which aspirin monotherapy was stopped without a substitute, higher rates of thrombotic events occurred (64,65). Of course, a patient group on aspirin monotherapy totally differs from the present patients receiving long-term VKA plus clopidogrel therapy. Nevertheless, in the WOEST trial, the AFCAS trial, and the Danish and German registries, there was no excess of stent thrombosis in the aspirin-free group (6,13-15). Therefore, it is debatable whether this

unopposed thromboxane-dependent platelet activation after stopping aspirin is clinically meaningful in the present patient population. It is possible that the negative impact of unopposed thromboxane-dependent platelet activation is overruled by the anticoagulant effect of VKA and the antiplatelet effect of clopidogrel.

The sixth unanswered question in patients on long-term VKA who received a coronary stent is: how should we treat patients after clopidogrel is discontinued (after 3, 6, or 12 months of treatment)? Do you treat patients with a combination of VKA and aspirin because of CAD, or is VKA monotherapy enough to protect patients against thrombotic events? In the absence of randomized trials, we turn to 2 large registries: a recently published Danish registry containing 8,700 patients and ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation), in which 4,804 patients taking VKAs were compared with 2,543 patients taking OAC plus aspirin. In both registries, the combination of
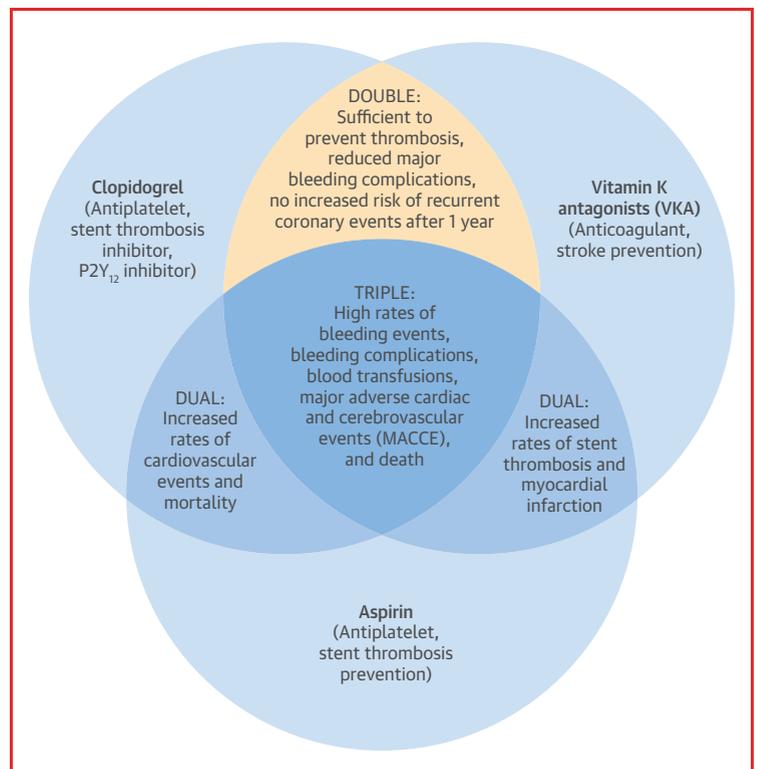
CENTRAL ILLUSTRATION Double and Triple Antiplatelet Therapy Risks in AF and PCI

Patients with atrial fibrillation (AF) who undergo percutaneous coronary intervention (PCI): combining antiplatelet and anticoagulant therapies in search of an optimal equilibrium in between bleeding risk on the one hand and thrombotic and thromboembolic risk on the other.

VKA and aspirin was associated with significantly increased risk for bleeding without a clear reduction of MACCE (66,67).

The seventh possible pitfall is that the guidelines recommend BMS placement in both elective and acute settings for AF patients with an indication for long-term VKA therapy (4,68). However, these recommendations were based upon expert opinion in the absence of data from randomized trials. A recent subanalysis of the WOEST trial shows no advantage for patients who received a BMS as compared with a DES. Moreover, the rate of TVR was significantly lower in patients treated with DES, despite the fact that baseline characteristics for this group were less favorable (such as a higher incidence of diabetes at baseline and more American College of Cardiology/American Heart Association type C lesions) (unpublished data). We also know that the rates of TVR and stent thrombosis are markedly lower after implantation of newer-generation DES, such as everolimus-eluting stents (69), and the difference in the rate of stent thrombosis after DES as compared to BMS seems to have disappeared with the newer-generation DES.

Finally, recent data suggest that 3 months of DAPT might be long enough in some cases instead of the standard 12 months. In the recent OPTIMIZE (Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice) trial, among 3,199 patients with stable CAD or low-risk ACS treated with zotarolimus-eluting stents, 3 months of DAPT was noninferior to 12 months, without significantly increasing the risk of stent thrombosis (70). Moreover, the EXCELLENT (Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting), PRODIGY (Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study), and RESET (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation) randomized trials also tested different durations of DAPT (3 or 6 months vs. 12 or 24 months) with multiple DES, and results did not show benefits favoring prolonged DAPT (71-74).

One can question if patients on long-term OAC might benefit from a shorter treatment with clopidogrel that would surely decrease bleeding risk in this patient group. But, before adopting a regimen containing 3 months of clopidogrel, some caution is needed. First, a cohort study containing 125,195 patients showed that the bleeding risk is the highest during the first 30 days of VKA therapy, with almost 1% of all new users admitted to a hospital for hemorrhage during this period (37). Second, it is unclear whether this applies to all DES, as zotarolimus-eluting stents were especially chosen in the OPTIMIZE and RESET trials because of their early vessel healing characteristics (70-74). Third, the OPTIMIZE trial mostly included patients with stable angina and low-risk ACS while excluding ST-segment elevation myocardial infarction patients (70). Therefore it might be too early to change the duration of routine clopidogrel administration to 3 months.

NEW MEDICATION, ONGOING TRIALS AND FUTURE PERSPECTIVES

Although dual therapy with VKA and clopidogrel probably presents a better option than triple therapy, there is still much room for improvement with regard to the prevention of both ischemic and bleeding events. Therefore, the search for newer and better antithrombotic medication and combinations of these drugs continues.

Over the last several years, numerous new medications have emerged to challenge the classics. In the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial evaluating 18,624 patients with ACS, the combination of ticagrelor (a reversible $P2Y_{12}$ inhibitor) and aspirin was superior to clopidogrel and aspirin (56). Administration of ticagrelor even led to a decrease in mortality. The TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38) trial showed that in 13,608 patients with ACS undergoing PCI, the combination of prasugrel (a more potent thienopyridine than clopidogrel but similarly an irreversible $P2Y_{12}$ inhibitor) and aspirin was more effective than clopidogrel and aspirin, but with an increased number of bleeding events (57).

Both prasugrel and ticagrelor seem to be good alternatives to clopidogrel in patients with AF undergoing PCI because they inhibit platelets more potently and show less interindividual variability than clopidogrel. But both the PLATO and TRITON-TIMI 38 trials excluded patients with VKA. In a prospective registry of 377 patients, the combination of prasugrel, aspirin, and VKA was used by 21 patients and showed a 4-fold increase in the risk of TIMI minor and major bleeding compared with a regimen of clopidogrel, aspirin, and VKA, without any significant difference in efficacy (75). We do not have any data yet on the combinations of VKA plus prasugrel, VKA plus ticagrelor, or triple therapy (VKA plus ticagrelor plus aspirin) in AF patients undergoing PCI, but one could reasonably fear that combining these more potent platelet inhibitors with VKA could lead to more bleeding events.

Over the last decade, non-VKA oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, and apixaban have been shown to offer advantages over VKA for stroke prevention in patients with AF (76-79). Their potential as antithrombotic therapy after ACS has as subsequently been investigated. The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis IN Myocardial Infarction trial, for example, showed that by adding low-dose rivaroxaban in 15,526 patients with a recent ACS, the composite endpoint of cardiac death, MI, and stroke was reduced, whereas the risk of major and intracranial bleeding was simultaneously increased (32). The APPRAISE 2 (Apixaban for Prevention of Acute Ischemic Events 2) trial, in which full-dose apixaban was added to dual antiplatelet therapy in patients with ACS, was halted prematurely, however, due to an excess in major bleeding events without a significant reduction in ischemic events (33). In the REDEEM (RandomizEd Dabigatran Etexilate Dose Finding Study in Patients With Acute Coronary Syndromes) trial, dabigatran in addition to DAPT also resulted in a dose-related increase in bleeding risk without reduction of ischemic clinical events (79).

In AF patients who need PCI, none of these NOACs has been tested yet. As demonstrated by all of these trials, finding the balance between reducing the risk of thromboembolic events without excessively increasing bleeding risk is difficult. The challenge of using NOACs in AF patients who need PCI is just as difficult. First of all, we encounter the problem of finding the optimal NOAC dose for this indication; and second, we have to ponder which $P2Y_{12}$ inhibitor to prescribe and whether or not to combine it with aspirin. PIONEER AF-PCI (An Open-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) is the first trial to address this issue, although the number of different possibilities to investigate seems almost unlimited (80). PIONEER AF-PCI is an innovative phase IIb clinical study investigating the safety and efficacy of rivaroxaban in AF patients undergoing PCI.

This study aims to include 2,100 patients to compare the safety of 2 rivaroxaban treatment strategies versus a dose-adjusted VKA treatment strategy. Patients will be treated for 12 months, and the primary endpoint is the composite of TIMI major bleeding, TIMI minor bleeding, and bleeding requiring medical attention (80). The RE-DUAL PCI (Randomized Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy Strategy with Warfarin in Patients with NVAF that have undergone PCI with Stenting) trial was also started recently. In this trial, the safety and efficacy of 2 dabigatran treatment strategies will be tested versus dose-adjusted VKA treatment (81). Unfortunately, the superior arm of the WOEST trial (VKA and clopidogrel) was left out of both trials (80,81). Another trial that is still recruiting patients is the ISAR TRIPLE (Intracoronary Stenting and Antithrombotic Regimen: 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 in which 600 patients are randomized to a 6-week versus a 6-month triple therapy regimen after DES implantation. The primary endpoint of ISAR TRIPLE is a net clinical benefit endpoint consisting of MACCE and major bleeding (82).

CONCLUSIONS

The efficacy of triple therapy (VKA, aspirin, and clopidogrel) in AF patients who need to undergo PCI with stent placement has never been proven, but this strategy increases bleeding risk significantly. New evidence, including a randomized controlled trial and a real-life nationwide registry of more than 12,000 patients, showed the great potential of the combination of VKA and clopidogrel without aspirin to improve clinical outcomes in comparison with triple therapy. Therefore, VKA combined with clopidogrel seems to be a reasonable alternative to triple therapy in patients on long-term VKA who undergo PCI and stenting.

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