

Triple therapy (aspirin, clopidogrel and oral anticoagulant) after percutaneous coronary intervention: another call for personalized medicine

Perkütan koroner girişimden sonra üçlü antitrombotik tedavi (aspirin, clopidogrel ve oral antikoagülan): Kişiyeye özel yaklaşım gereksinimi

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ABSTRACT

Studies indicate that 5-7% patients undergoing percutaneous coronary intervention (PCI) have an indication for anticoagulation therapy. Most commonly atrial fibrillation (AF) is the indication. These subjects require triple therapy with aspirin, clopidogrel, and an oral anticoagulant (OAC). Several questions, concerns and challenges exist regarding the duration, benefit, risks and alternatives related to triple therapy. These questions constitute a moving target with recently approved antiplatelet and anticoagulant agents. This brief review will summarize the current literature regarding triple therapy, potential solutions that can mitigate the formidable risk of bleeding. Arising from that discussion, a logical consensus can be developed that should be applicable to studies with novel agents that interfere with homeostasis. The ultimate goal is to enhance cardiovascular outcome and decrease thrombotic and bleeding complications.

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Key words: Triple therapy, dual antiplatelet therapy, percutaneous coronary stenting, atrial fibrillation, bleeding complications

ÖZET

Perkütan koroner girişim (PKG) yapılan hastaların %5-7'sinin bir antikoagülan tedavi indikasyonu bulunmaktadır. Atriyal Fibrilasyon (AF) tanılı hastalarda PKG ihtiyacı en yaygın indikasyonu oluşturmaktadır. Bu olgularda, aspirin, klopidogrel ve bir oral antikoagülan (OAK) ile üçlü tedaviye ihtiyaç duyulmaktadır. Üçlü tedavinin süresi, yararları, riskleri ve alternatifleri bakımından birçok soru, kaygı ve zorluklar bulunmaktadır. Bu sorular, yeni onaylanan antiplatelet ve antikoagülan ajanlarla beraber yenilenen yaklaşımlar oluşturmaktadır. Bu kısa derleme üçlü tedaviye ve korkulan kanama riskini azaltacak potansiyel çözümleri içeren güncel literatürü özetleyecektir. Bu tartışmadan yola çıkılarak, antikoagülanlar ve platelet inhibitörleri dahil hemostazı etkileyen yeni ajanlarla yapılan çalışmalardan bahsedilecektir. Amaç uygulanabilir olacak mantıklı bir görüş birliği oluşturmaktadır. Esas hedef tromboza bağlı kardiyovasküler olayları önlerken oluşabilecek kanama komplikasyonlarını azaltmaktır. (*Anadolu Kardiyol Derg* 2013; 13: 486-94)

Anahtar kelimeler: Üçlü tedavi, ikili antiplatelet tedavi, perkütan koroner stentleme, atriyal fibrilasyon, kanama komplikasyonları

Introduction

Treatment of significant coronary artery disease (CAD) with percutaneous coronary intervention (PCI) frequently utilizes stent placement. Serious complication of stent thrombosis can lead to myocardial infarction (MI) and increase the mortality and morbidity. Dual antiplatelet therapy (DAPT) with aspirin and

clopidogrel has become the recommended treatment for the patients undergoing coronary stenting including those with or without acute coronary syndromes (ACS) (1).

On the other hand, studies indicate that 5-7% patients undergoing PCI have a standing indication for anticoagulation therapy (2), which is mostly the presence of atrial fibrillation (AF). These subjects require triple therapy with aspirin,



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clopidogrel, and oral anticoagulation (OAC). Several questions, concerns and challenges exist regarding the duration, benefit, risks and alternatives related to triple therapy stemming from the dreadful complication of bleeding (Fig. 1). The questions constitute a moving target with recently approved antiplatelet and OAC agents.

This brief review will summarize the current literature regarding the triple therapy, potential solutions that can prevent the formidable risk of bleeding. Although there is consensus about the indication for DAPT, there is little evidence about the optimal duration of triple therapy. For instance, in patients surviving non-ST-segment elevation ACS, 1 year of DAPT is routine clinical practice (3). If an indication for anticoagulation simultaneously exists, should this patient receive 1 year of triple therapy? Such an approach will undoubtedly increase the bleeding risk. This has been established in the large trials with clopidogrel in ACS (4, 5) as well as in AF (6). Long-term studies are needed to find the optimal duration of triple therapy.

Antithrombotic therapy for atrial fibrillation

AF is the most common cardiac arrhythmia and is associated with a small but significant incidence of stroke and systemic thromboembolism (7). The CHADS₂ score is commonly used to assess risk of stroke (8). The CHA₂DS₂-VASc score takes into account the extent of vascular disease, intermediate age, and sex (9). It has been shown to have better discrimination of stroke risk particularly in low-risk patients. It is well established that OACs reduce the incidence of stroke and systemic embolism in AF patients (10). The American College of Cardiology/ American Heart Association (ACC/AHA) guidelines recommend OAC therapy with warfarin for those patients with at least 1 additional risk factor for stroke and suggest the use of aspirin only for those at low risk for stroke such as patients without risk factors (11).

In patients without a prior thromboembolic event, the risk of stroke or systemic embolism is relatively constant over time; 1.4%/y on warfarin and 2.4%/y on aspirin and clopidogrel, as reported in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W (ACTIVE-W) trial (12). Although there are no data available concerning the risk of stroke or systemic embolism with AF after a PCI, it is not likely that it is increased substantially beyond that seen with AF alone unless there has been a recent embolic or a new cardiovascular event, such as a ST-elevation myocardial infarction (STEMI).

Antithrombotic therapy in patients undergoing PCI

Pathophysiology and the mechanisms of thrombus formation differ between that associated with AF and that of CAD and stent thrombosis. Plasma factors (i.e., coagulation factors) are more important in the development of thromboembolic events during AF and cellular factors (i.e., platelets) are more important in the pathophysiology of atherothrombotic events (13). Consequently, anticoagulant therapies are more beneficial for prevention of thromboembolism in patients with AF and

antiplatelet agents are of greater benefit in the prevention of ischemic events, including stent thrombosis, in patients undergoing PCI. Therefore, patients with AF who also undergo PCI with placement of a coronary stent have a higher risk for both thromboembolic events and stent thrombosis if they are not on both anticoagulant and antiplatelet therapy (14).

The incidence of stent thrombosis averages 1-2% over the first year but is greatest in the first month regardless of the type of stent used (15, 16). Stent thrombosis is associated with a mortality of 10-20% and a MI rate of 30-70% in those with early or late stent thrombosis (17). The greatest risk factor for stent thrombosis is premature discontinuation of DAPT (aspirin plus clopidogrel) especially before 6 months (18). Current ACC/AHA guidelines recommend DAPT in patients with an STEMI for at least 1 year for bare metal stent (BMS) and drug eluting stent (DES) and in patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI) receiving a BMS, DAPT should be given for 1 month and preferably for 1 year (19, 20).

Antithrombotic therapy for patients with AF undergoing PCI

The choice of antithrombotic medications for patients with AF undergoing PCI is dependent on the balance between the risk of stroke/emboli, recurrent ischemic events, stent thrombosis, and major bleeding (21). Although there are wide variations in type and duration of therapy in practice, triple therapy (oral anticoagulation and DAPT with aspirin and clopidogrel) is the most common treatment regimen in this setting. Since, it is a commonly observed problem in the clinical setting, several organizations offer potential solutions and recommendations. For instance, a survey of the Society for Cardiac Angiography and Interventions (SCAI) membership was conducted recently. Members of the organization were asked regarding patients with AF taking warfarin. More than 168 members expressed their opinion. After a BMS implantation, the majority of interventionalists (86%) preferred to use triple therapy for 1 month followed by warfarin and aspirin. Obviously, situation changes in case of a DES. In patients receiving a DES, a greater duration of triple therapy was preferred, with 47.4% recommending triple therapy for 6 months or longer. Other combinations such as oral anticoagulation, and 1 antiplatelet agent or DAPT alone were less commonly selected. These findings confirm the wide variability in practice and the lack of consensus regarding the best antithrombotic therapy for these patients. The final recommendation will depend on the ongoing studies with triple therapy.

The definition and avoidance of major bleeding

Bleeding is considered the most important complication of triple therapy. The combination of antiplatelet therapy with warfarin significantly increases the bleeding risk, for instance when aspirin is combined with warfarin for AF, it has been shown to be increased 43% in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (22) to 80% in a

large Danish registry (23). The bleeding risk becomes formidable in these studies. For DAPT, the increase is 370% (23). The confounding condition is that the extent and the definition of bleeding in these studies are not uniformly distributed. Obviously, the most devastating bleeding event is an intracranial hemorrhage. In some series, this accounted for 90% of the deaths from warfarin-associated hemorrhage in the first 30 days after initiation of therapy and accounted for the majority of disability among survivors (24).

There are numerous definitions of bleeding, but Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe/life threatening bleeding and Thrombolysis in Myocardial Infarction (TIMI) major bleeding are most commonly used. The unified finding between the definitions of bleeding complications is that major bleeding is associated with increased short and long-term mortality after PCI (25).

Major bleeding is a significant predictor of worse outcome. The question is whether we can effectively identify the subjects who are at risk for major bleeding. Risk factors for bleeding from warfarin have been described previously. Lip et al. (26) utilized a previously derived bleeding risk score; HAS-BLED [Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly] for risk stratification of bleeding. Clinical investigators applied this risk score to patients with AF in the Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation (SPORTIF) III and V trials (26, 27). When compared with other scores, it performed modestly better. Importantly, aspirin or nonsteroidal anti-inflammatory drugs increased the risk nearly 2-fold (HR=1.98). The risk factors identified by multivariable analysis in this study were aspirin use, creatinine clearance <50 mL/min, age >75 years, diabetes, or left ventricular dysfunction. Tighter control of the INR with levels between 2 and 2.5 when on triple therapy has been shown to reduce bleeding complications without an increase in major adverse cardiac events compared with those who did not maintain an INR within this range (28).

We need novel biomarkers and genetic tests that can discriminate subjects who are at increased risk for major bleeding from subjects with higher risk of thrombosis. Such an approach can help the clinician to predict the timing of the bleeding complication and to tailor the management after stent implantation accordingly. For instance, cumulative bleeding risk with both OACs and antiplatelet agents increases in direct relation to the duration of treatment. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W (ACTIVE-W) trial, the risk of major hemorrhage was similar for OACs (2.21%/y), aspirin, and clopidogrel (2.42%/y) (12). Although the risk for bleeding on warfarin is greatest in the first month after initiation, it remains steady afterward. The bleeding risk for aspirin and clopidogrel in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) trial was greatest in the first month

and declined over the next year (29). Patients who did not have a major bleeding episode in the first year had no increased bleeding with continued treatment compared to aspirin alone (30). This is in contrast with novel P2Y12 receptor inhibitors, which was associated with increased rates of spontaneous bleeding over time (31).

Not surprisingly, the risk of bleeding rises with an increased number of antithrombotic agents (32, 33). Not all studies however have shown an increased bleeding risk on triple therapy (34). In a meta-analysis of available trials, the risk of major bleeding on triple therapy was estimated to be 2.2% at 1 month (35). This risk of major bleeding increases at 1 year to 4–12%, emphasizing that the longer the duration of triple therapy, the more the bleeding. Limiting the duration of triple therapy when possible should be considered as a key step to reducing overall bleeding risk.

New agents

The limitations of currently available antiplatelet agents fueled the search for new platelet inhibitors. ‘Prasugrel’ and ‘ticagrelor’ are the novel P2Y12 receptor antagonists. These novel antiplatelet drugs have more potent platelet inhibitory effects compared with clopidogrel in patients with a high thrombotic risk such as ACS in preventing recurrent ischemic events. They also significantly reduce stent thrombosis compared with clopidogrel (36, 37). As expected, novel agents come with certain drawbacks. For instance, in the setting of coronary stenting they are associated with an increased risk of spontaneous bleeding (36, 37). Prasugrel has been shown to cause more intracranial bleeding than clopidogrel in patients with prior cerebrovascular disease, and elevated mortality rates have been reported after intracranial hemorrhage among patients treated with ticagrelor (36, 37). Thus, the duration (and/or dosing) of antiplatelet therapy may be lowered to minimize the extra bleeding hazard and they should not to be used in combination with OACs until adequate safety data are available.

The Food and Drug Administration (FDA) recently approved dabigatran, an oral direct thrombin inhibitor that does not require laboratory monitoring of anticoagulation intensity, for the prevention of stroke and embolism in patients with AF based on the results of the 18 113 patient multicenter RE-LY trial (38). In this trial, the small subset of patients on triple therapy with dabigatran did not appear to have less bleeding than those on triple therapy with warfarin. However, no firm recommendations can be made at this time concerning triple therapy with dabigatran, given the absence of safety and efficacy data in patients undergoing PCI. Given the lack of data to suggest harm, it is not unreasonable to use dabigatran in place of warfarin.

Oral direct factor Xa inhibitors, rivaroxaban and apixaban, are also being investigated for the treatment of patients with AF, although these have not been approved for this indication. No data exist concerning Rivaroxaban use with antiplatelet agents in patients with AF. Apixaban showed a trend toward a reduction in ischemic events in patients with ACS but also demonstrated

an increased bleeding risk particularly in those taking dual antiplatelet therapy (39). Surely, new trial results are needed before we can recommend novel antiplatelet agents in the setting of triple therapy.

General recommendations for triple therapy

The general principle guiding the use of triple therapy is to choose a treatment strategy that is tailored to the individual patient, taking into consideration the anticipated risk of an adverse event, particularly major bleeding. In each patient on warfarin, the indication for DAPT should be judged at the moment of decision for stent implantation. Novel biomarkers of thrombosis and bleeding can help the clinician to risk stratify the individual patient and to modify the duration of the triple therapy.

Balancing risk

Triple therapy constitutes a significant challenge for the clinician to balance the potential risk and the benefit. The risk is greatest in the first month for bleeding and stent thrombosis, whereas it remains constant over time for stroke and embolization. All patients regardless need DAPT for at least 1 month. In addition, patients presenting with a STEMI, NSTEMI or ACS are at higher risk for thrombotic complications and DAPT is recommended for 1 year in these patients (20). Therefore, we should avoid factors that can increase the risk of bleeding. For instance, according to Clopidogrel optimal loading dose Usage to Reduce recurrent Events-Optimal ANtiplatelet Strategy for interventionS (CURRENT-OASIS 7) trial, low dose aspirin should be used in the setting of triple therapy in order to avoid excess bleeding (40).

Currently available scoring systems can help us to individualize the antithrombotic regimen. In patients at very low risk of stroke or embolism (CHADS₂=0-1), DAPT without warfarin is probably preferable and is consistent with the current ACC/AHA guidelines (11). On the other hand, patients with higher risk of stroke (CHADS₂ ≥2) (but not at high risk of bleeding) require triple therapy. Furthermore, in those at higher risk of both stroke and bleeding, the duration of therapy should be reduced in proportion to the bleeding risk.

In patients with BMS who are at low risk for stent thrombosis or in patients who are at high risk for bleeding, it may be reasonable to use triple therapy for one month followed by one antiplatelet agent and warfarin thereafter. From the SCAI survey, this appears to be the most commonly utilized strategy. The optimal duration of DAPT in patients who have undergone stent implantation is still not fully established but a general principle would be that the greater the risk of stent thrombosis, the longer the duration. However, bleeding risk is the most fearsome complication while deciding the duration of DAPT.

Several studies attempt to resolve this question. ZEST/REAL-LATE is a large study, which randomized stable patients 1 year after drug-eluting stent implantation (41). Subjects were randomly assigned to longer duration of clopidogrel plus aspirin

or to aspirin alone (41). The results at 19 months displayed that there was a non-significant increase in the composite risk of more MI, stroke, or death from any cause in the patients who had continued their clopidogrel treatment compared to control group. The control subjects stopped clopidogrel at random assignment 1 year after implantation.

Finally, the three adverse events of triple therapy (stroke/embolism, stent thrombosis, major bleeding) are associated with a risk of death that occurs among one-fourth to one-half of patients (2, 14, 21). Many patients consider a large stroke to be a more devastating complication due its impact on long-term disability, and thus should be weighted more heavily than stent thrombosis and bleeding when considering the balance of risk and benefit (Fig.1).

Vascular access and procedural considerations

Radial access has gained considerable interest and is being increasingly used as the preferred vascular access site given the reported lower risk of major bleeding (42). The choice of the procedural anticoagulant is important, with lower rates of bleeding reported with the use of bivalirudin and the use of femoral closure devices, and increased rates reported with the use of glycoprotein IIb/IIIa agents (43).

PCI and stent selection

Careful consideration should be made to the necessity of PCI with stent placement because many stable angina patients can be managed on maximal medical therapy, thus avoiding the bleeding risks associated with triple therapy. Despite public awareness about coronary stents, balloon angioplasty alone can at times achieve an acceptable result. In such patients, the risk of restenosis is higher, but when an acceptable or "stent-like" result occurs, thienopyridine may not be required resulting in a reduction in risk of bleeding that may outweigh the increased risk of restenosis.

When stent placement is required during a PCI, and an OAC is absolutely required long term, placement of a BMS is generally

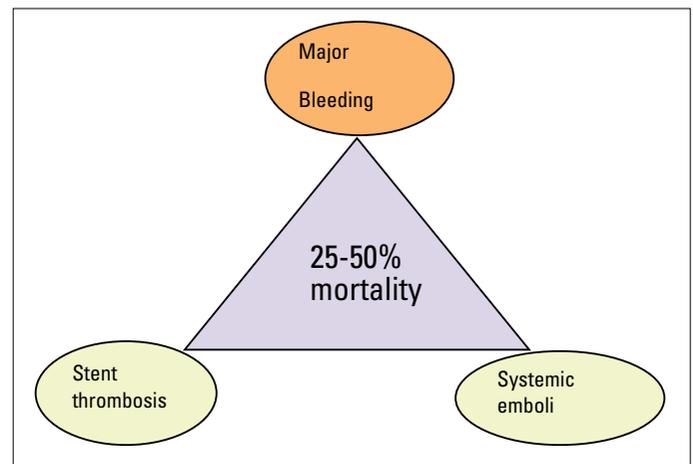


Figure 1. Deadly triad of triple therapy; 3 adverse events to be considered in selecting triple therapy are associated with a risk of death that occurs among one-fourth to one-half of patients (2, 14, 21)

preferred over a DES. Because the risk of stent restenosis is greatest in long lesions, small vessels, and in patients with diabetes, the degree of benefit of a lower restenosis rate with DES in patients without these factors may be exceeded by the increased risk of bleeding with the longer duration of triple antithrombotic therapy. Although the ACC/AHA guidelines recommend 12 months of DAPT, there are preliminary data indicating that stent thrombosis may be very low when DAPT is discontinued 6 or perhaps even 3 months after placement of a second-generation DES, such as the everolimus or zotarolimus-eluting stent (44, 45). Based on emerging evidence that first-generation stents appear to have a greater late stent thrombosis rate, second-generation stents are preferred in patients who need a DES and triple therapy during follow-up. The third-generation stents, especially the biodegradable stents, are being designed to further reduce stent thrombosis.

Specific recommendations

Table 1 shows recommendations based on the opinion of the authors considering the best available information (2). The

Table 1. General recommendations considering triple therapy (2)

Low-dose (≤ 100 mg) aspirin should be used.
A proton pump inhibitor should be given to reduce the risk of GI bleeding.
Avoid concomitant use of nonsteroidal anti-inflammatory agent use.
Clopidogrel is the thienopyridine of choice in combination with aspirin and warfarin. Prasugrel and ticagrelor cannot be recommended with warfarin until the safety of such triple therapy is demonstrated.
Warfarin should be dose adjusted and closely monitored to maintain the INR between 2 and 2.5.
Triple therapy use and duration should depend on the benefit and risk balance.
GI - gastrointestinal, INR - international normalized ratio

authors recognize that several potential options are reasonable and that in individual patients, the optimal regimen will differ. Based on the European Society of Cardiology AF guideline (46), Table 2 displays antithrombotic strategies following coronary artery stenting in patients with AF.

Recently resulted and ongoing randomized trials of triple therapy

The current concerns about bleeding and stent thrombosis complications stimulate upcoming trials after coronary stent implantation. Large studies are addressing the optimal duration of DAPT in patients after stent deployment. For instance, ISAR-SAFE study attempts to answer the question with 6000 patients after DES. Subjects receive DAPT for 6 versus 12 months. The study primary end-point at 15 months includes stroke, major bleeding and death. On the other hand, the DAPT trial is comparing 12 versus 30 months of DAPT in 20 000 patients with BMS or DES. The end-points include stent thrombosis, major bleeding, and major cardiovascular/cerebrovascular events. It is

Table 2. Antithrombotic strategies following coronary artery stenting in patients with AF (2, 46)

Low stroke risk (CHADS₂=0) and any stent thrombosis or bleeding risk:
BMS: DAPT with aspirin and clopidogrel or prasugrel for 1 month and preferably for 12 months. DES: DAPT with aspirin and clopidogrel or prasugrel for 12 months or longer.
Moderate/high stroke risk (CHADS₂ >1), low stent thrombosis risk and low bleeding risk:
BMS: Triple therapy for at least 1 month then OAC+single antiplatelet for 12 months. DES: Triple therapy for at least 6 months then OAC+single antiplatelet for 12 months.
Moderate/high stroke risk and high stent thrombosis risk and low bleeding risk:
BMS: Triple therapy for at least 6 months then OAC+single antiplatelet for 12 months. DES: Triple therapy for 12 months.
Moderate/high stroke risk and any stent thrombosis risk and high bleeding risk:
BMS: Triple therapy for at least 1 month then OAC+single antiplatelet for 12 months. DES: not recommended.
Longer durations of DAPT up to 12 months may be reasonable in patients undergoing stenting for STEMI and NSTEMI ACS and are at high risk of thrombotic events with a low risk of bleeding.
After 12 months, warfarin alone should be given indefinitely. In patients at high risk for atherothrombotic events including stent thrombosis, continued single antiplatelet therapy with warfarin should be considered after 12 months.
ACS - acute coronary syndrome, AF - atrial fibrillation, BMS - bare metal stent, DAPT - dual antiplatelet therapy, DES - drug eluting stent, NSTEMI - Non-ST-elevation myocardial infarction, OAC - oral anticoagulation, STEMI - ST elevation myocardial infarction

likely that novel agents will be tested for the same purpose in the coming year.

The novel agents bring a moving target and more questions. There are 3 registered ongoing randomized clinical trials of triple therapy in patients undergoing PCI. The number of trials will likely increase with the introduction of novel antithrombotic agents. The What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting Trial (WOEST) results are newly demonstrated in European Society of Cardiology Congress 2012; 573 patients already treated with OAC for AF or mechanical valves and undergoing coronary stenting were randomized to either OAC plus clopidogrel or to triple therapy. The primary end-point was any bleeding over 1 year. The dual therapy of clopidogrel and OAC in coronary stent patients causes less bleeding with no increased risk of stent thrombosis, stroke or MI than the triple therapy of aspirin, clopidogrel and OAC. WOEST is the first ever study to demonstrate that it is safe to omit aspirin in these patients, and that the results could have major treatment implications. The Triple Therapy on Anticoagulation After Drug-Eluting Stent Implantation Trial (ISAR-TRIPLE) plans to enroll 600 patients and will compare a short course of triple therapy (6 weeks) with a long course (6 months) followed by aspirin and warfarin. The primary end-point will be the composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months. The Anticoagulation in Stent Intervention Trial (MUSICA-2) will randomly assign 304 patients with low to moderate stroke risk ($CHADS_2 \leq 2$) to DAPT or triple therapy. The primary end-point will be death, MI, stroke, embolization, or stent thrombosis at 12 months. In addition, there are a number of on-going registries. These randomized trials should help to define some of the potential treatment options for these patients in the future, though the sample sizes are modest.

Personalized medicine to direct triple therapy

Most of the current knowledge about triple therapy comes from randomized trials performed in patients undergoing PCI. Even though randomized trials have become the standard way of answering clinical questions, CAD is a complex trait, with well-documented genetic and ethnic components. Unlike Mendelian diseases that are associated with a single gene, most common complex traits (such as thrombosis and bleeding) are caused by the non-linear interaction of numerous genetic and environmental risk factors. Furthermore, clinical trials often fail to replicate findings in different populations. One potential explanation for inconsistency between different studies is that the risk of complications is not based on a single clinical factor of major effect, but on interactions among several pathophysiological pathways with multiple genes and environmental risk factors. For instance, several genetic polymorphisms affect the metabolism of the antithrombotic medications. Conversion of clopidogrel, which is a pro-drug to its active metabolite is dependent on the cytochrome P450 (CYP) enzymes, especially CYP2C19 (47) and variants in the CYP2C19 gene are responsible for diminished or

enhanced capacity for conversion of clopidogrel to the active metabolite. Poor metabolizers are at a 2- to 5-fold increased risk for repeat ischemic event and poor clinical outcomes despite antiplatelet therapy (48). CYP2C9 is another enzyme involved in the hepatic biotransformation of clopidogrel to its active metabolite and CYP2C9 loss of function variants lead to decreased clopidogrel-mediated platelet inhibition (49). In addition, polymorphisms in CYP2C9 and vitamin K epoxide reductase complex subunit 1 (VKORC1) genes change warfarin pharmacokinetics and pharmacodynamics, respectively (50). We propose that using advanced models to characterize the association between multiple genetic and environmental factors and measures of disease related complications i.e. bleeding and thrombosis. The detection of genetic, ethnic and environmental interactions associated with complications will be a difficult challenge for the epidemiologist and the clinician. Rather than relying solely on the results of a clinical trial, we should understand characteristics of the populations and the individual patients.

Conclusion

This review provides a guide to clinicians faced with the difficult decision of when and how long to administer triple antithrombotic therapy to a patient with AF who has undergone a coronary stent placement. The recommendations are largely based on expert opinion rather than strong registry and randomized trial data. These recommendations are based on the estimation of the risk of stroke, stent thrombosis, and major bleeding and are meant to be a guide to assist in the assessment of individual patients. Obviously, new data are needed to cover all bases. A number of randomized trials are ongoing or are planned, and until the trial results are available, sound clinical judgment is necessary to optimally treat such patients.

Abbreviations

ACC/AHA: American College of Cardiology / American Heart Association
ACS: Acute coronary syndrome
ACTIVE-W: Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-W trial
AF: Atrial fibrillation
BMS: Bare metal stent
CAD: Coronary artery disease
CHARISMA: Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
CYP: Cytochrome P450
DAPT: Dual antiplatelet therapy
DES: Drug eluting stent
FDA: Food and Drug Administration
GUSTO: Global Use of Strategies to Open Occluded Coronary Arteries
INR: International normalized ratio
ISAR-TRIPLE: The Triple Therapy on Anticoagulation After

Drug-Eluting Stent Implantation Trial

MUSICA-2: The Anticoagulation in Stent Intervention Trial

NSTEMI: Non- ST- elevation myocardial infarction

OAC: Oral anticoagulation

PCI: Percutaneous coronary intervention

RE-LY: Randomized Evaluation of Long-Term Anticoagulation

Therapy

SCAI: Society for cardiac angiography and interventions

SPORTIF: Stroke Prevention Using an ORal Thrombin Inhibitor in Atrial Fibrillation

STEMI: ST-elevation myocardial infarction

TIMI: Thrombolysis in Myocardial Infarction

VKORC1: Vitamin K epoxide reductase complex subunit 1

WOEST: What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting Trial

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