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Managing Antiplatelet Therapy and Anticoagulants in Patients with Coronary Artery Disease and Atrial Fibrillation

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Abstract

Oral anticoagulation (OAC) is essential in patients with atrial fibrillation (AF). Interestingly coronary artery disease coexists in 20–30% of these patients.[1,2] Balancing the risk of bleeding and thromboembolism is very important for the management of patients on OAC, especially than when such patients require percutaneous coronary intervention (PCI). Lack of data and clear societal guidelines for peri-procedural and post-procedural management of anticoagulated patients has resulted in diverse clinical practices among clinicians, hospitals, and countries. Furthermore with expanding number of available oral antiplatelet and anticoagulant agents, the uncertainty regarding optimal combination therapy in this growing pool of the patients with overlapping clinical indications is also growing. Given the high proportion of patients with atherothrombosis and requiring OAC for conditions particularly like AF, it is important that physicians are aware of the clinical implications and management of these overlapping syndromes.

In this article we discuss; this evolving dilemma of peri-procedural and post-procedural management of anticoagulated patient's, burden of the disease, available data, risk factors that could identify high risk patients and propose a well-balanced management strategy.

Introduction

Long-term oral anticoagulation (OAC) is the cornerstone in the treatment of patients with atrial fibrillation (AF) at moderate to high risk of stroke, those with prosthetic heart valves, cardiogenic thromboembolism, recent deep vein thrombosis or pulmonary embolism. Approximately 70–80% of all patients in AF have an indication for continuous OAC, and coronary artery disease coexists in 20–30% of these patients.[1,2] Balancing the risk of bleeding and thromboembolism is crucial in the management of patients on OAC, and this is never more apparent than when such patients require percutaneous coronary intervention (PCI). The periprocedural management of anticoagulated patients is very important, but clinical practice varies widely between clinicians, hospitals, and countries, driven by a lack of data on which to draw guidance. Furthermore as the number of available oral antiplatelet and anticoagulant agents continue to grow, so does the uncertainty regarding optimal combination therapy in this growing pool of the patients with overlapping clinical indications. Given the high proportion of patients with atherothrombosis and requiring OAC for conditions particularly like AF, it is important that physicians are aware of the clinical implications and management of these overlapping syndromes.

Key Words:
Lariat, Embolic Stroke, Anticoagulant Therapy.

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None.

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Burden of the Atrial Fibrillation, Valvular Heart Disease and Venous Thromboembolism Disease

The prevalence of atrial fibrillation (AF) in the United States is approximately 6 million patients and is on the rise.[3] More than 17 million patients have coronary artery disease (CAD), and over 6 and 8 million Americans, respectively, have suffered a stroke or have peripheral arterial disease.[4] The prevalence of AF in patients with established atherothrombosis (11.7%) or risk factors for atherothrombosis (6.2%) is substantially higher compared with the general population (2.3%).[5,6] Another challenging patient population is those with valvular heart disease who underwent mechanical valve replacement. Approximately 90000 valve substitutes are now implanted in the United States and 280 000 worldwide each year; approximately one fourth of the US valve replacements are mechanical valves requiring long term OAC.[7] Venous thromboembolism (VTE) causes significant morbidity and mortality with an estimated annual incidence of 900,000 patients with clinically evident VTE in the U.S., resulting in an estimated 300,000 deaths from PE.[8] Keeping in mind the burden of various diseases requiring long term OAC, it is estimated that 5–7% of patients undergoing percutaneous coronary interventions (PCI) have indications for chronic oral anticoagulant therapy.[9, 10]

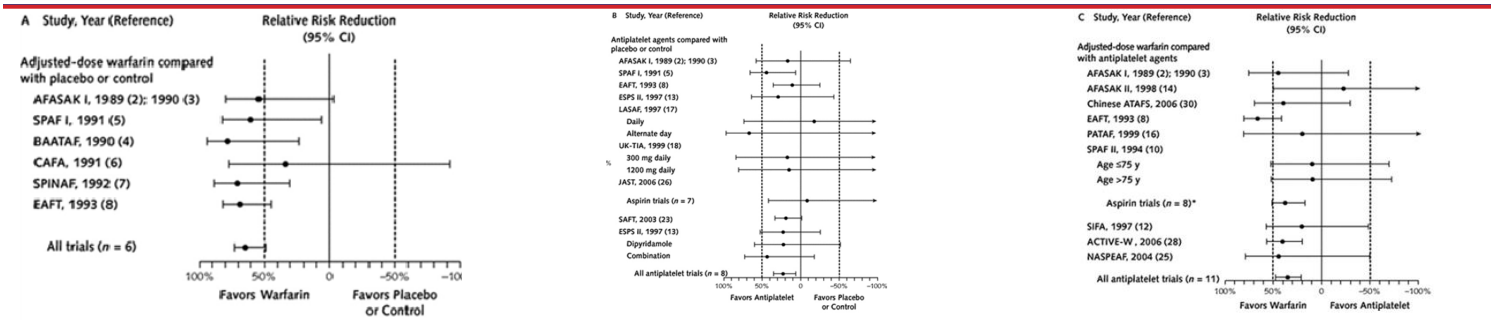

Figure 1: **Reveals relative effects of antithrombotic therapies on all types of strokes from randomized trials in patients with atrial fibrillation. Horizontal lines represent 95% CIs around point estimates. A. Adjusted-dose warfarin compared with placebo or no treatment in 6 randomized trials**

Understanding the Problem

The mechanisms of thrombus formation differ between that associated with thromboembolic diseases like AF and that of coronary artery disease 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.[11] Consequently, oral anticoagulant therapies are mainstay of treatment for stroke prevention in atrial fibrillation (AF), as-well as prevention of pulmonary embolism in the recent deep vein thrombosis or pulmonary embolism and antiplatelet agents are of greater benefit in the prevention of ischemic events, including stent thrombosis, in patients undergoing PCI.

AF is the most common cardiac arrhythmia and is associated with a small but significant incidence of stroke and systemic thromboembolism.[12] It is well established that oral anticoagulants reduce the incidence of stroke and systemic embolism in these patients.[13] A meta- analysis of 29 trials showed that warfarin reduced stroke by 64% as compared with placebo and by 39% as compared with aspirin in patients with non-valvular AF[14] (Figure-1). Furthermore several trials including ACTIVE-W have confirmed the superiority of warfarin in reducing embolic events over dual antiplatelet therapy (DAPT) with aspirin and clopidogrel in patients with both paroxysmal and sustained AF and at least 1 additional stroke risk factor[15] (Figure-2).

As a result, the ACC/AHA guidelines recommend oral anticoagulant 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.[12] Dual antiplatelet therapy (DAPT) is the standard of care to reduce recurrent ischemic events after acute coronary syndrome (ACS) and to prevent stent thrombosis after percutaneous coronary intervention (PCI). Furthermore dual antiplatelet therapy has also been proven to be superior in terms of safety and efficacy when compared with anticoagulation with Warfarin following coronary stenting. Data from Stent Antithrombotic Regimen Study (STARS) trial, in which 1653 patients who had successful placement of the stent were randomly assigned to one of three regimens: aspirin alone (557 patients), aspirin and warfarin(550 patients), and dual antiplatelet therapy (DAPT) with aspirin and ticlopidine (546patients), revealed that DAPT reduced the occurrence of death, target lesion revascularization, stent thrombosis, and recurrent MI at 30 days from 3.6% with aspirin alone and 2.7% for aspirin and warfarin compared to only 0.5% for aspirin and ticlopidine16 (Figure-3). Because clopidogrel, a second-generation thienopyridine, has fewer adverse effects than ticlopidine, such as thrombotic thrombocytopenic purpura and severe neutropenia, it rapidly became the thienopyridine of choice.[17,18] Current ACC/AHA guidelines recommend DAPT in patients with an STEMI for at least 1 year for BMS and DES. In patients with unstable angina or NSTEMI receiving a BMS, DAPT should be given for at least 1 month and preferably for 1 year.[19,20] In patients who receive an elective DES, the current recommendations are for one year of DAPT.

Three antithrombotic drug combinations have been used most in practice: triple therapy (oral anticoagulation and dual antiplatelet therapy with aspirin and clopidogrel), oral anticoagulation, and 1 antiplatelet agent (aspirin or clopidogrel), or rarely, DAPT alone without oral anticoagulants. Although there are wide variations in type and duration of therapy in practice, triple therapy is the most common treatment regimen in this setting. Several studies demonstrate that the risk of bleeding rises with an increased number of antithrombotic agents. In one study of 21,443 elderly patients followed on average for 22 months after an acute MI, bleeding was 1.7 times more frequent with DAPT and 1.9 times more frequent with aspirin plus warfarin when compared with aspirin monotherapy.[21] Similarly, in a nationwide registry of 40,812 patients with acute MI in Denmark, the risk of bleeding was 2.6% for aspirin, 4.6% for clopidogrel, 4.3% for DAPT, 5.1% for aspirin plus an oral anticoagulant, 12.3% for clopidogrel plus an oral anticoagulant, and 12.0% for triple therapy over a mean follow-up of 16 months[22] (Figure-4). Hence patients taking combination of oral anticoagulants with aspirin and clopidogrel ("triple therapy") pose a significant dilemma for the cardiologist because of the increased risk of major bleeding.

In one study among patients on triple therapy with aspirin, clopidogrel, and warfarin, major bleeding occurred in 4.7%, and approximately 50% of these patients died within 6 months.[23] In a meta-analysis involving 13 retrospective studies (Figure-5A) and registries assessing antithrombotic regimens in patients with AF undergoing PCI risk of major bleeding was 1.5% at 30 days and 5.2% at 1 year with triple AT (aspirin + warfarin + clopidogrel/ticlopidine). Dual antiplatelet therapy (aspirin + clopidogrel/ticlopidine) was associated with 2.4% annual risk of major bleeding.[24] Similarly, in another meta-analysis involving 9 randomized controlled trials (Figure-5B), patients with triple antithrombotic regimen had significant reduction in ischemic stroke (odds ratio [OR] is 0.29, 95% confidence interval [CI] is from 0.15 to 0.58; and P = 0.0004) as compared with dual antiplatelet therapy. While there was a two-fold

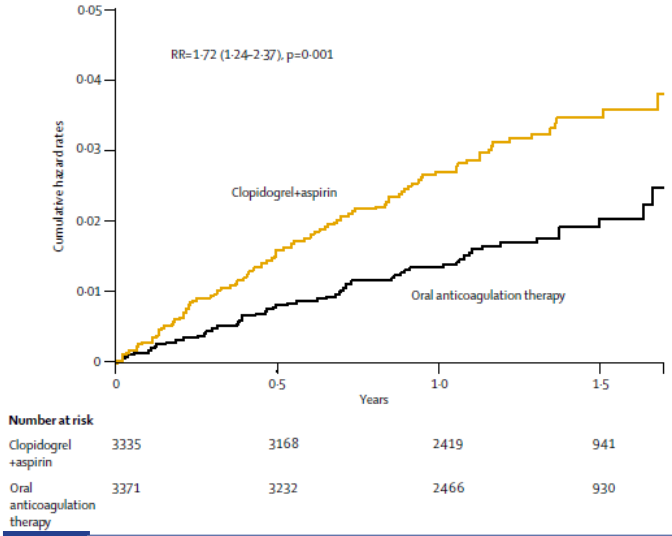

Figure 2: **Depicts that compared with clopidogrel plus aspirin, oral anticoagulation therapy reduced all strokes. (RR 1.72, 95% CI 1.24–.37; p=0.01) indicating that oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke, especially in those already taking oral anticoagulation therapy.**

increased risk of major bleeding associated with triple antithrombotic regime (OR 2.00, 95% CI 1.41 to 2.83; and P < 0.0001). The overall incidence of death (OR 1.20, 95% CI 0.63 to 2.27, and P = 0.56) and myocardial infarction (OR 0.84, 95% CI 0.57 to 1.23; and P = 0.38) was comparable between the two regimens.[25] Both studies confirm the cardiovascular benefits of triple antithrombotic regimen by reducing ischemic stroke risk, but also demonstrated its increased risk of major bleeding.

Major bleeding is a serious complication that is associated with increased morbidity and mortality particularly when it occurs shortly after a stent procedure. Despite different bleeding definitions, both access site and non-access site bleeding has been observed across all the major trials in patients undergoing PCI. In fact, in one of a major meta-analysis using combined dataset from the REPLACE-2 (Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events), Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), and HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trials in 17,393 PCI patients, non-access site bleeding after PCI was found to be common, representing approximately two-thirds of all TIMI bleeding events, and was found to be associated with a 4-fold increase in 1-year mortality.[26] Furthermore, similar results have been found in other studies indicating a strong relationship between early bleeding and 1 year mortality. Results from a major meta-analysis that included 5,384 patients from 4 randomized placebo-controlled trials: ISAR-REACT, SWEET, SMART-2, and REACT-2, revealed that the 30-day occurrence of bleeding independently predicted 1-year mortality by a Cox proportional hazards model, indicating a strong relationship between the 30-day frequency of bleeding and 1-year mortality after PCI [27](Figure-6).

Bleeding severity also has been found to be directly related to mortality. In a meta-analysis involving about 26500 patients from the multicenter international GUSTO IIb, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT), and the Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) A and B trials were studied. The study demonstrated a relationship between bleeding severity and worsening 30 day mortality.[28] Interestingly, the studies aimed to investigate the long-term prognosis of patients with in-hospital major bleeding after primary PCI also show significantly increased 3-year rates of morbidity and mortality[29,30] (Figure-7).

Management

Managing the patients with AF requiring oral anticoagulants with aspirin and clopidogrel needs a thoughtful balancing act between risk of stroke or systemic embolism, risk of stent thrombosis and recurrent ischemic events as well as risk of bleeding.

Arguably, the 3 key issues appear to be:

1. Whether or not to interrupt OAC for the procedure
2. The choice of long term antithrombotic therapy that follows PCI
3. How best to modify the procedure to ensure optimal safety

Whether or Not to Interrupt OAC for The Procedure

Current guidelines offer limited guidance on long-term OAC during the peri-PCI period. Strategies like temporary replacement of warfarin by dual antiplatelet drug therapy and temporary adjustment of warfarin dosing to reach a perioperative INR of 1.5–2.0 have been proven to result in more adverse effects and inadequate for PCI or stroke prevention in AF respectively.[31,32,33] This view is supported by data showing that non-use of OAC markedly increases mortality in patients with AF after acute myocardial infarction.[34,35,36] The most common practice is to offer "bridging" with either unfractionated or low molecular weight heparin (LMWH) to cover the temporary discontinuation of OAC, if the risk of thromboembolism is considered high. While this practice makes sense and appears to be logical based on the competing pathophysiologies, this approach is based on circumstantial evidence and there are no large randomized trials to support the recommendation. Furthermore, studies have shown that patients with ACS and on home warfarin are significantly less likely to undergo coronary angiography and PCI and their waiting times

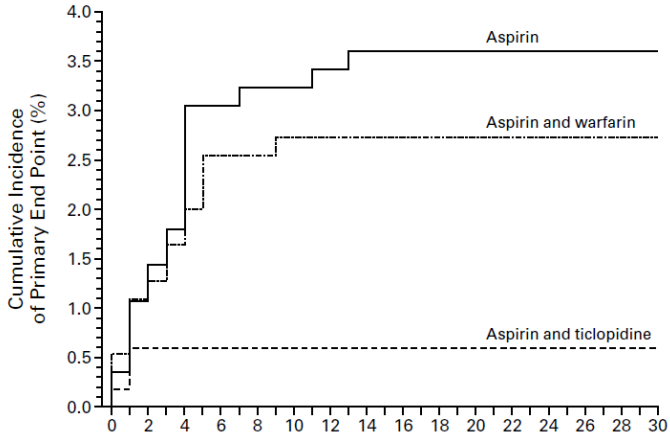

Figure:3 **1653 patients who had successful placement of the stent were randomly assigned to one of three regimens:aspirin alone (557 patients), aspirin and warfarin(550 patients), or aspirin and ticlopidine (546patients). The figure shows cumulative Incidence of the primary end point in the Three Treatment Groups. DAPT reduced the occurrence of death, target lesion revascularization, stent thrombosis, and recurrent MI at 30 days from 3.6% with aspirin alone and 2.7% for aspirin and warfarin to 0.5% for aspirin and ticlopidine.**

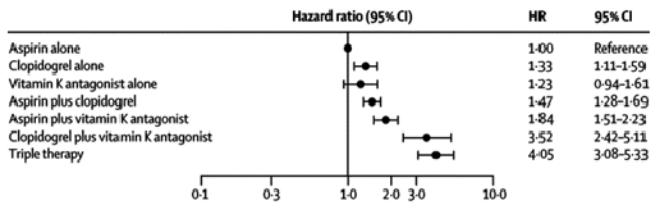

Figure:4 Reveals adjusted risk of non-fatal and fatal bleeding in 40,812 patients treated with antithrombotic drugs after first myocardial infarction HR=hazard ratio. Aspirin monotherapy is used as the reference. The risk of bleeding was 2.6% for aspirin, 4.6% for clopidogrel, 4.3% for DAPT, 5.1% for aspirin plus an oral anticoagulant, 12.3% for clopidogrel plus an oral anticoagulant, and 12.0% for triple therapy over a mean follow-up of 16 months.

for these procedures are longer than in patients not on warfarin.[37] The general perception that warfarin should be discontinued a few days prior to PCI and the periprocedural INR level should fall below therapeutic range (2.0) may contribute to these delays.

Interestingly, studies show that the incidence of bleeding or thrombotic complications is not related to peri-procedural INR levels, and propensity score analyses suggested that the bridging therapy with either unfractionated heparin or LWMH, to cover the temporary discontinuation of OAC increases the risks of peri-procedural bleeding and access site complications.[34,38,39] Supporting this view, recent findings suggest that uninterrupted anticoagulation with warfarin may be a better alternative to heparin bridging in catheter interventions with a favorable balance between bleeding and thrombotic complications.[60,61,62] Data from a major prospective multicenter European registry (Atrial Fibrillation undergoing Coronary Artery Stenting-AFCAS Registry) that recruited 963 patients with AF undergoing coronary stenting to compare the safety of uninterrupted anticoagulation (UAC), indicate that UAC does not increase perioperative complications during coronary stenting and is a simple and cost-effective alternative to conventional heparin bridging[40] (Figure-10).

Furthermore, studies have indicated advantages of PCI with UAC that includes prevention of the transient pro-thrombotic state due to proteins C and S suppression caused due to warfarin reinitiation, minimal wide and long lasting fluctuation in INR following warfarin interruption and effect of warfarin can be easily overcome by FFP or activated clotting factors II, VII,IX and X.[40,41,42]

In the European Society of Cardiology (ESC) guidelines for the management of valvular heart disease, continuation of OAC at modified doses is recommended for the majority of patients who undergo cardiac catheterization.[43] Similarly in the consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions, the UAC strategy is recommended as the preferred strategy for AF patients at moderate to high risk of thromboembolism.[44] For patients admitted with acute coronary syndrome, the risk of bleeding vs. thromboembolism becomes more complex, as these patients often require bivalirudin (a direct thrombin inhibitor) or glycoprotein IIb/IIIa inhibitors (GPI). The consensus document suggests stopping the OAC on admission in this circumstance. Exception to this may be patients at a very high risk of thromboembolism, such as those with mechanical mitral valves or recurrent venous thromboembolism, where uninterrupted OAC may be preferable to the potential risk of bleeding with interruption and heparin bridging.[44]

Choice of Long Term Antithrombotic Therapy that Follows PCI

Acute coronary syndrome patients presenting with acute ST-

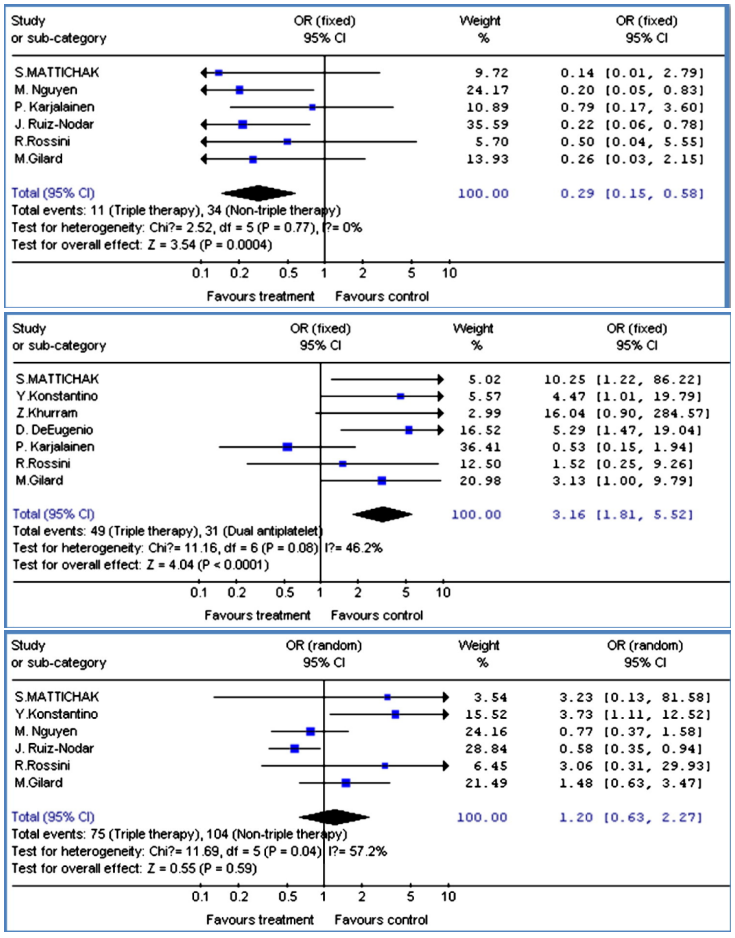

Figure: 5B Shows meta-analysis involving 9 randomized controlled trials. (a) Patients with triple antithrombotic regimen had significant reduction in ischemic stroke (odds ratio [OR] is 0.29, 95% confidence interval [CI] is from 0.15 to 0.58; and P = 0.0004) as compared with dual antiplatelet therapy.(b) While there was a two-fold increased risk of major bleeding associated with triple antithrombotic regime (OR 2.00, 95% CI 1.41 to 2.83; and P < 0.0001).(c) The overall incidence of death (OR 1.20, 95% CI 0.63 to 2.27, and P = 0.56) and myocardial infarction (OR 0.84, 95% CI 0.57 to 1.23; and P = 0.38) was comparable between the two regimens

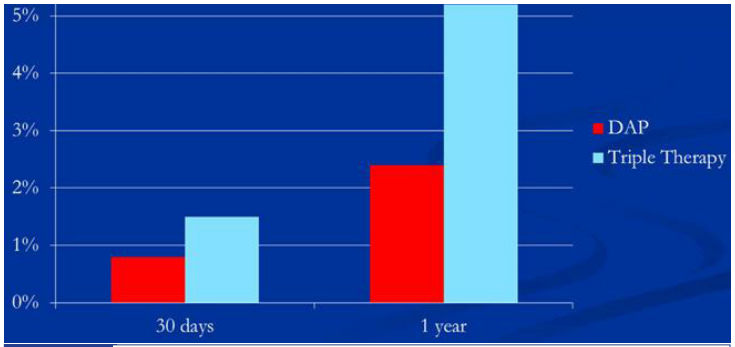

Figure: 5A Reveals results of the meta-analysis involving 13 retrospective studies and registries assessing antithrombotic regimens in patients with AF undergoing PCI, risk of major bleeding was 1.5% at 30 days and 5.2% at 1 year with triple AT (aspirin + warfarin + clopidogrel/ticlopidine). Dual antiplatelet therapy (aspirin + clopidogrel/ticlopidine) was associated with 2.4% annual risk of major bleeding.

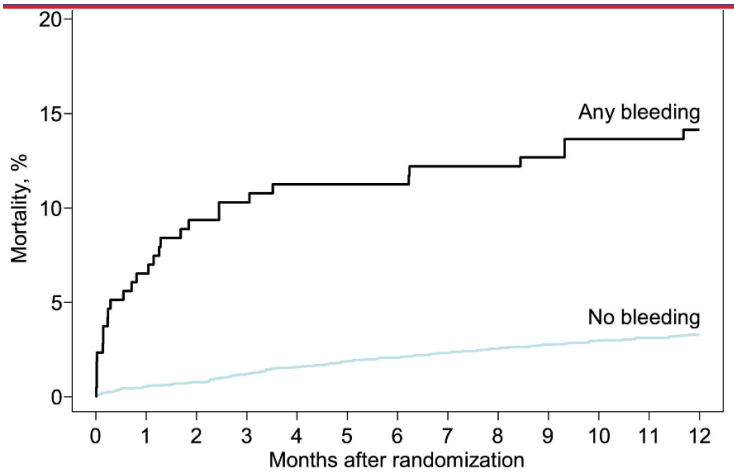

Figure:6 **Depicts. Kaplan-Meier curves of 1-year mortality among 5,384 patients from 4 randomized placebo-controlled trials. The 1-year mortality was 14.1% (n = 30) among patients in whom bleeding occurred within the 30 days after PCI versus 3.3% (n = 167) among patients who had no bleeding within the 30 days (OR 4.75, 95% CI 3.34 to 6.76, p < 0.001).**

elevation myocardial infarction (STEMI) are increasingly managed with primary PCI with additional combined antithrombotic therapy regimes.[19, 20] Those presenting with non-ST-elevation acute myocardial infarction (NSTEMI) are also managed with combined antithrombotic and anti-platelet therapy, as an early invasive revascularization strategy, is often employed based on guideline recommendations.[19,20]

The long-term results of stent usage have been blighted by the dual problem of in stent restenosis (ISR) and stent thrombosis. In particular, the increasing use of drug-eluting stents (DES) to minimize ISR necessitates long-term dual antiplatelet therapy with aspirin plus a thienopyridine (at present most frequently clopidogrel) to reduce the risk of early and late stent thrombosis. Current ACC/AHA guidelines recommend DAPT in patients with an STEMI for at least 1 year for DES and BMS.[19, 20]

As noted before, the results from ACTIVE-W trials demonstrated that combined aspirin– clopidogrel therapy cannot replace OAC in stroke prevention in patients with AF.[15] Several observational studies on clinical practice support this conclusion also in patients with AF after coronary stenting.[34, 35] Likewise OAC alone is insufficient to prevent stent thrombosis[45,46,47,48] making management of patients with Afib patients requiring stent very complicated. At present, in patients on OAC therapy, the additional use of dual antiplatelet therapy (triple therapy) seems to be the best option to prevent stent thrombosis and thromboembolism. Data from CRUSADE Registry indicates that Triple Therapy is the commonest regimen used in the setting of atrial fibrillation patients requiring PCI.[49] Similarly data from Society for Cardiac Angiography and Interventions survey (2011) reveal that 86% of interventionists prefer Triple Therapy for 1 month followed by warfarin and aspirin in case of bare-metal stent and 47.4% recommend at least 6 months of Triple Therapy after DES implantation.

As per consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions,[44] in case of elective PCI Clopidogrel 75 mg daily should be given in combination with OAC plus aspirin 75–100 mg daily for a minimum of 1 month after implantation of a BMS, but longer with a DES (at least 6 months) and clopidogrel 75 mg daily (or alternatively aspirin 75–100 mg daily, plus gastric protection with a PPI) may be continued depending on the bleeding and thrombotic risks of the individual patient. In case of the AF patients presenting with Non-ST elevation ACS like NSTEMI and unstable angina with or without PCI and at moderate to high risk of stroke it is recommended to continue/give anticoagulation therapy in addition to dual antiplatelet therapy with aspirin plus clopidogrel. However in the acute setting, patients are often given aspirin, clopidogrel, heparin (whether UFH or an LMWH, enoxaparin) or bivalirudin and with some frequency a GPIIa/IIIb inhibitor (GPI). Given the risk of bleeding with such combination antithrombotic therapies, it is recommended to stop OAC therapy, and administer antithrombins or GPIs only if INR ≤ 2. As per consensus paper, in the setting of acute STEMI with primary PCI and AF, it is recommended that patients should be given aspirin, clopidogrel, and heparin (UFH). When patients have a high thrombus load, GPIs may be given as a 'bail out' option. As an alternative to heparin plus GPI, bivalirudin might be used and has a superiority in bleeding risk as demonstrated in the ACUITY and HORIZONS-AMI trials. Given the risk of bleeding with such combination antithrombotic therapies, it may be prudent to stop OAC therapy. Ideally, GPIs would not be considered if except only in a 'bail out' option. Detailed recommendations from consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions are depicted in the Table-1.

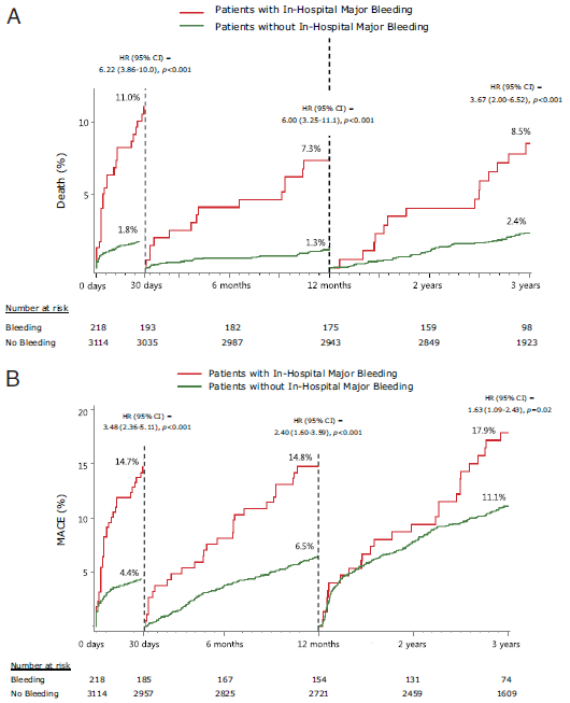

Figure:7 **Results of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial involving 3,345 patients with primary PCI. The rates of mortality and MACE were significantly higher in patients with in-hospital major bleeding (IHMB) within each time interval. The deleterious effect of major bleeding was observed within 1 month, between 1 month and 1 year, and between 1 and 3 years. IHMB was an independent predictor of mortality (hazard ratio: 2.80; 95% confidence interval: 1.89 to 4.16, p < 0.0001) at 3-year follow up.**

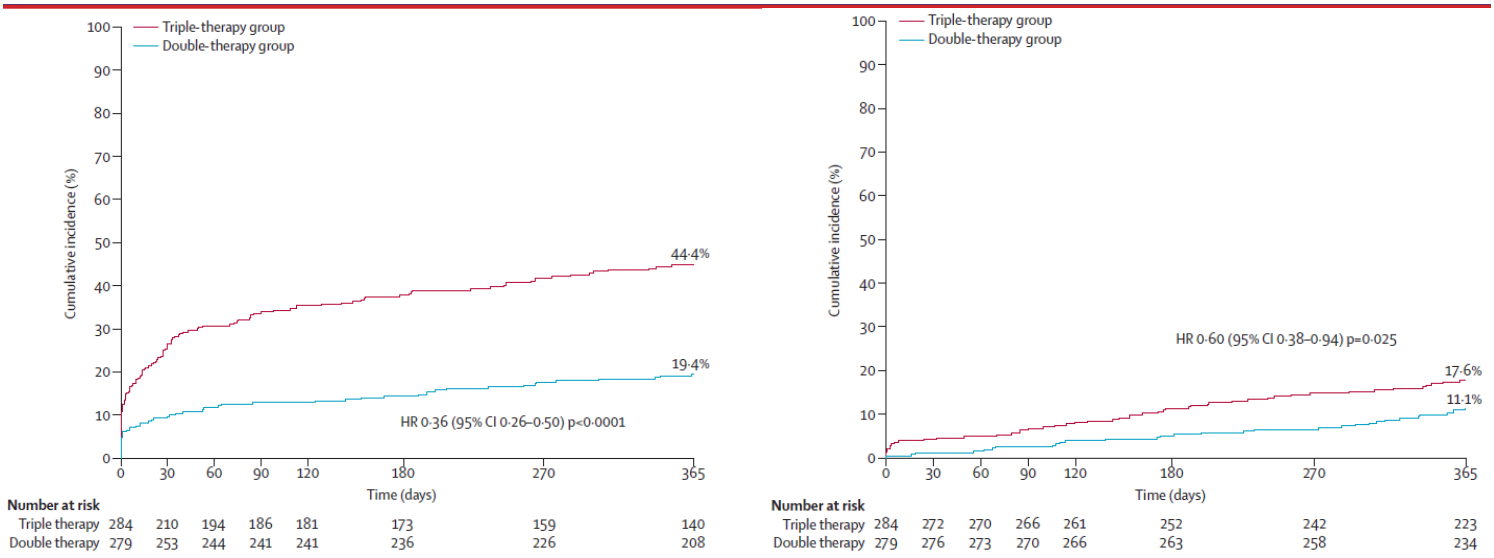

Figure 8: **Results of the WOEST (The What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) study, an open-label, randomized, controlled trial done at 15 sites in the Netherlands and Belgium involving patients taking oral anticoagulants who underwent PCI. 573 patients were enrolled and 1-year data were available for 279 (98·2%) patients assigned double therapy and 284 (98·3%) assigned triple therapy. (A). Incidence of the primary endpoint (any bleeding), bleeding episodes were seen in 54 (19·4%) patients receiving double therapy and in 126 (44·4%) receiving triple therapy (hazard ratio [HR] 0·36, 95% CI 0·26–0·50, p<0·0001).**

Dual Therapy (Warfarin+ Clopidogrel) Vs. Triple Therapy

Results from the single center WOEST trial involving 573 patients who underwent PCI with a mean follow up of 1 year clearly show that use of dual therapy (Warfarin and clopidogrel without aspirin) was associated with a significant reduction in bleeding complications with no increase in the rate of thrombotic events were observed50. Furthermore use of triple therapy was associated with higher mortality and morbidity (Figure-8). Similar observations were made in previous smaller studies51. Although data on the efficiency and safety of warfarin plus clopidogrel combination are limited, but this combination may be an alternative in patients with high bleeding risk and/or absent risk factors for stent thrombosis. Future multi-center trials will need to confirm these results.

Modifying the Procedure and Bleeding Avoidance Strategies to Ensure Optimal Safety

For optimal outcome, a delicate balance is needed between the prevention of thromboembolism, against recurrent cardiac ischemia or stent thrombosis, and bleeding risk, to individualize treatment options thus avoiding regimented common protocol. Following considerations could be used while managing a patient on anticoagulation requiring PCI.

Identify the High Risk Patient

Thromboembolism, stent thrombosis and peri-procedural bleeding are all described as complex phenomenon and dependent on several independent predictors.[68,69] (Table-2) Identification of the AF patients undergoing PCI who are at high risk for thromboembolism, stent thrombosis and peri-procedural bleeding is very important for the optimal outcome. Interestingly Faxon et al identifies patients with AF at moderate to high risk of stroke (CHADS-2 score≥1) undergoing PCI into three groups based on the risk for stent thrombosis (ST) and bleeding.[67] Low ST and low bleeding risk group, high ST and low bleeding risk group and high ST and high bleeding risk group. The management plan from each group is depicted in figure-9.

Choosing the Right Stent and Procedure

Recommendations from consensus paper of the Working Group on Thrombosis of the ESC, endorsed by the European Heart Rhythm Association and European Association of Percutaneous Cardiovascular Interventions,[44] clearly state that the use of DES of first and second generation, due to the prolonged need of dual antiplatelet therapy, should be avoided in patients with an indication for long-term OAC and high bleeding risk. However DES is recommended in the patients with high risk of stent restensois and

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) by European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI)**

Haemorrhagic Risk	Clinical Setting	Stent Implanted	Recommendation
Low or intermediate	Elective	Bare metal	1 month: triple therapy of warfarin(INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0 - 3.0) alone
	Elective	Drug eluting	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75mg/day Up to 12 months: combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day (or aspirin 100 mg/day)[a] Lifelong: warfarin (INR 2.0 - 3.0) alone
	ACS	Bare metal/ drug eluting	6 months: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75mg/day Up to 12 months: combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day (or aspirin 100 mg/day)[a] Lifelong:warfarin (INR 2.0 - 3.0) alone
High	Elective	Bare metal[b]	2 - 4 weeks: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/ day + clopidogrel 75 mg/day Lifelong:warfarin (INR 2.0 - 3.0) alone
	ACS	Bare metal[b]	4 weeks: triple therapy of warfarin (INR 2.0 - 2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day up to 12 months: combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day (or aspirin 100 mg/day); mg/day);[a] Lifelong:warfarin (INR 2.0 - 3.0) alone

INR international normalized ratio; acute cornary syndrome
[a]combination of warfarin (INR 2.0 - 2.5) + clopidogrel 75mg/day may be considered as a alternative
[b]Drug eluting sents should be avoided

where a significant benefit is expected DES when compared with BMS. Furthermore, as more studies emerge suggesting shorter duration of DAPT therapy is safe and effective in reducing stent thrombosis with second generation drug eluting stents, cardiologists will be able to reduce their patient exposure to either dual therapy or triple therapy. Reduction in the need for DAPT to 3-6 months for 2nd generation DES will make DES a more accessible option in even higher risk patients. Finally, in the extremely high risk bleeding patient, balloon angioplasty can also be considered when the angiographic result after balloon angioplasty is acceptable. In some cases also coronary artery bypass graft (CABG) might be favored over PCI if the patient is a reasonable surgical candidate otherwise.

Wise Selection of Access Site

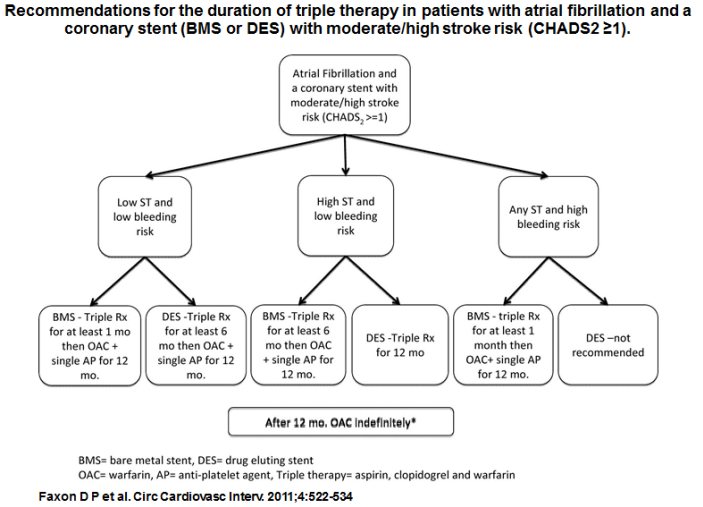

Figure 9: **Recommendations for the combination and duration of triple therapy in patients with atrial fibrillation and a coronary stent (BMS or DES) with moderate/high stroke risk (CHADS2≥1. BMS indicates bare metal stent; DES, drug-eluting stent; OAC, warfarin; AP, antiplatelet agent; and triple therapy, aspirin, clopidogrel, and warfarin. In patients at high risk for atherothrombotic events including stent thrombosis, continued single antiplatelet therapy with warfarin should be considered after 12 months. The authors used the following average crude estimates of risk for each adverse outcome listed below (low and high) to be:**
• Stroke risk (CHADS2_1) on warfarin average 1.5%(1.0% for CHADS2_1–7% for CHADS2_5–6) per year (or adjusted stroke rates from 1.95%/y to _12.5%/y).
• Stent thrombosis (first year) on DAPT_1.5% (1–5%) but 5- to 36-fold higher for premature discontinuation within the first month, and 2.5- to 5-fold if between 1 and 6 months. On DAPT the risk is greatest in the first month.
• Major bleeding requiring hospitalization on triple therapy_6–15%/y; warfarin and 1 antiplatelet agent_6–12%/y; and on either DAPT or warfarin alone 2.5–4%/y. The rate is highest within the first 30 days after the procedure.

Several independent studies indicate that vascular access site selection may have a great impact on bleeding complications. Meta-analyses of randomized trials and registry studies clearly reveals that radial artery access is associated with a reduced risk of access site bleeding and other vascular complications.[52,53,54,55] Furthermore femoral access was an independent predictor (hazard ratio of 9.9) of access site complications in 523 warfarin-treated patients.[55] On the basis of current evidence, a radial approach should be always considered in anticoagulated patients, since haemostasis is rarely an issue with this access site.

Avoidance Of Newer Anti-Platelet Agents Like Prasugrel And Ticagrelor In Triple Therapy

Results from TRITON–TIMI 38 and PLATO trials, reveal higher rates of bleeding with newer anti-platelet agents prasugrel and ticagrelor respectively.[56,57,58] Therefore avoidance of newer anti-platelet agents like prasugrel and ticagrelor in the patients on OAC in the setting of ACS or requiring PCI is reasonable if a strategy of triple therapy is being pursued. Use of the newer antiplatelet therapy in setting of dual therapy with warfarin or novel oral anticoagulants are still being investigated. Please see below.

Gastric Acid Suppression With PPIs

Gastric protection with proton pump inhibitors (PPIs) is considered useful in patients on triple therapy and those prone to develop gastrointestinal bleeding (elderly, patients with a history of ulcer disease or prior gastrointestinal bleeding).[59]

Avoid Gpis

Several studies indicate that the GPI use is associated with a 3–13-fold risk of early major bleeding in warfarin-treated patients who undergo revascularization in the form of PCI.[60,61,62] In general, GPIs seem to increase major bleeding events irrespective of peri-procedural INR levels and should be used with some caution in this patient group and probably avoided if use is not indicated due to massive intraluminal thrombi. Furthermore, GPIs add little benefit in terms of reduction of ischemic events in patients with stable angina and troponin-negative ACS.[63,64]

Use of Bivalirudin

Results from HORIZONS-AMI, and ACUITY trials reveal

Table 2: Risk factors associated with an increased risk for stroke/thromboembolism, peri -procedural bleeding[68] and stent thrombosis

Thromboembolism/ Stroke	Stent thrombosis	Peri-pocedural bleeding
Diabetes mellitus	1. Patient-related factors relating to increased thrombogenecity. Smoking, Diabetes mellitus, Chronic kidney disease, Acute coronary syndrome presentation, High post-treatment platelet reactivity, Premature discontinuation or cessation of dual antiplatelet therapy	Advanced age (>75years)
Previous stroke, transient ischemic attack, or embolism	2. Surgical procedures (unrelated to the PCI) Diffuse coronary artery disease with long stented segments, Small vessel disease, Bifurcation disease, Thrombus-containing lesions, Significant inflow or outflow lesions proximal, or distal to the stented segment	Female gender
Heart failure or moderate–severe left ventricular dysfunction on echocardiography (e.g. ejection fraction ≤40%)	3. Stent-related factors Poor stent expansion, Edge dissections limiting inflowor outflow, Delayed or absent endothelialization of stent struts, Hypersensitivity/inflammatoryand/ or thromboticreactions to DES polymers , Strut fractures, Late malposition/aneurysm formation, Development of neoatherosclerosis within stents with new plaque rupture	Renal failure
Vascular disease		Uncontrolled hypertension
Hypertension	Years	Low body weight. Patients (n)
Female gender		History of bleeding.
Renal failure	2006	Right heart catheterization
Mitral stenosis or prosthetic heart valve	2008	Anemia
		Use of GPIIb-IIIa antagonists
		Triple therapy

superiority of bivalirudin usage in the setting of primary PCI and non-ST-elevation (NSTE) ACS over combination of heparin plus GPI in terms of lesser morbidity and mortality. Furthermore data from studies support reduced both access site and non-access site bleeding with bivalirudin usage compared to heparin plus GPIs.[65,66] Although data on bivalirudin in AF patients, especially in the setting of concomitant anticoagulation with an OAC is lacking based on the current available date it is likely to be a safer and effective option in the setting of acute coronary syndromes.

Ongoing Clinical Trials

Currently several planned trials are undergoing in this field. PIONEER AF-PCI is a 3 arm study involving 2100 patients randomized to.

(a) Rivaroxiban 15mg PO daily and clopidogrel 75mg PO daily

(b) Initial period of rivaroxaban 2.5mg PO BID and dual antiplatelet therapy followed by rivaroxaban 15mg PO daily and low dose aspirin.

(c) Initial period of dose-adjusted warfarin and dual antiplatelet therapy followed by dose-adjusted warfarin and low dose aspirin.

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"), is designed to evaluate the efficacy and safety of Dabigatran in patients with nonvalvular atrial fibrillation (NVAF) who have undergone PCI. MUSCA 2 trail will compaire dual antiplatelet therapy with triple antiplatelet therapy in patients with non-valvular atrial fibrillation undergoing PCI who are at low to moderate risk of stroke (CHADS-2 ≤ 2). The ISAR-TRIPLE is a randomized, open-label trial that examines the restriction of clopidogrel therapy from 6 months to 6 weeks after DES implantation in the setting of concomitant aspirin and oral anticoagulant. Patients are randomized in a 1:1 fashion to either 6-week or 6-month clopidogrel therapy. The primary end point is a composite of death, myocardial infarction, definite stent thrombosis, stroke, or major bleeding. The result of these trials will be critical in assessing safety and efficacy of treating these complex patients with competing indications for their disease treatments.

Conclusion

Balancing the risk of bleeding, thromboembolism and the risk for acute and late stent thrombosis in the patient who has a clear indication for oral anticoagulation and has undergone percutaneous coronary intervention, continues to remain a complex and difficult dilemma for clinicians. The need to address competing indications is further magnified in the setting of acute coronary syndromes. Risk stratification of patients, utilization of direct thrombin inhibitors, avoidance of GPIs, carefully choosing POBS, BMS, and second generation DES are critical in reducing bleeding complications. Limiting the length of exposure to DAPT in the setting of anticoagulation is also a mainstay of reducing risk. Dual therapy (single non-aspirin anti-platelet therapy coupled with anticoagulation, warfarin or a NOAC) may be a viable and safer alternative without compromising risk or long term stent outcomes. Further trials will hopefully answer whether this strategy and the concept of uninterrupted anticoagulation will be ideal approaches to treating these complex patients.

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