# TRIPLE ANTITHROMBOTIC THERAPY FOR ATRIAL FBRILLATION AND CORONARY STENTS

**Dusmuratova D.A.**
Department of faculty therapy Andijan state medical institute, Uzbekistan

**Abstract:** Triple antithrombotic treatment for arterial fibrillation and coronary stents Triple treatment (TT) alludes to the concurrent utilize of an verbal anticoagulant (OAC), such as warfarin, and double antiplatelet treatment (DAPT), such as acetylsalicylic corrosive (ASA) furthermore clopidogrel. 1 The foremost common clinical sign for TT is patients with arterial fibrillation (AF) who have intense coronary disorder (ACS) or who have experienced percutaneous coronary mediation (PCI) with stent addition, which accounts for around 5% to 8% of all patients who experience [1]. There's constrained prove to direct clinicians on endorsing TT. As such, it is diffcult to appraise the beneft of TT over DAPT or double treatment (ie, an OAC also a single antiplatelet specialist) in these patients. As anticipated, TT carries the next hazard of dying than double treatment or DAPT do. 3 Encourage, the chance of dying increments with proceeded use. 4 Owing to restricted prove and the complexity of this regimen, TT ought to as it were be endorsed after meeting with a cardiologist. Of note, the endorsing designs of cardiologists for these patients might change owing to the need of defnitive information. For case, a later investigation of antithrombotic endorsing in patients with AF after PCI inside one Canadian cardiology middle concluded that less than half of patients gotten TT and roughly one gotten non–evidence-based therapies.

5 The show article surveys the writing on TT, centering on choices with respect to choice of anticoagulant or antiplatelet treatment and length, and traces how essential care prescribers can screen TT, communicate the method of reasoning for and length of TT to patients, and decrease the chance of dying (Box 1).

***Case description:*** Mrs K.A., an 75-year-old lady known to you, presents to your clinic with shortness of breath, weariness, and a "racing heart," which begun roughly 2 days prior. An electrocardiogram confrms AF with a heart rate of 120 beats/min. You audit her chart to choose an specialist for AF stroke anticipation and are reminded that she had a non-ST-segment rise This article is qualified for Mainpro+ certifed Self-Learning credits. myocardial dead tissue 2 months back, which was overseen with 2 drug-eluting stents. She was endorsed 90 mg of ticagrelor twice every day for 12 months, 81 mg of ASA day by day for life, 50 mg of metoprolol twice every day, 10 mg of ramipril every day, and 40 mg of atorvastatin every day. Her past restorative history incorporates hypertension, sort 2 diabetes mellitus, dyslipidemia, and osteoarthritis. Her other drugs incorporate 500 mg of metformin twice every day, 650 mg of acetaminophen twice day by day, and 20 mg of paroxetine once day by day, which was begun amid menopause for hot fashes. Mrs K.A. could be a non-smoker and exceptionally seldom expends liquor. She has no portability issues and lives freely in a condominium with her spouse.

Box 1. Down to earth tips for observing and communicating the method of reasoning for and term of antithrombotic TT to patients

When treatment is started, archive the taking after within the patient's chart (paper or electronic therapeutic record): • sign for and planning length of TT [2];

• the recommended target INR (eg, 2.0-2.5, 2.0-3.0) in the event that warfarin is utilized;

• informational for step-down treatment, along side term of treatment;

• HAS-BLED score and reversible chance variables to address (audit at each consequent visit whereas taking TT); and



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• the aiming term of proton pump inhibitor utilize, in case taking for gastroprotection Incorporate the taking after on the medicine name
• enlightening for length of TT (eg, "continue until [date], at that point stop") Quiet instruction:
• Emphasize the expecting length of TT and energize the understanding to report any bleeding
• Guarantee the understanding gets it which antithrombotics are to be proceeded when TT is total (particularly with ASA, because it is accessible over the counter)
• Taught the persistent to maintain a strategic distance from over-the-counter items that can increment the hazard of dying (eg, NSAIDs, vitamin E, high-dose omega-3 [3-4 g/d], G characteristic wellbeing items [eg, ginkgo, ginseng, garlic])

ASA—acetylsalicylic acid; HAS-BLED—hypertension with a systolic blood pressure >160 mm Hg, abnormal renal or liver function, stroke (caused by a bleed), bleeding, labile INR, elderly (age >65 y), drugs (ASA, NSAIDs) or alcohol (≥8 drinks/wk); INR—international normalized ratio; NSAID—nonsteroidal anti-inflammatory drug; TT—triple therapy. Mrs K.A.'s later research facility comes about uncovered a hemoglobin A1c level of 7.8% and a low-density lipoprotein cholesterol level of 2.6 mmol/L. Her total blood tally comes about, renal work, and liver protein levels were inside ordinary limits. Within the clinic nowadays, her body mass list is 26 kg/m2 and her blood weight is 124/82 mm Hg. Her CHADS2 (congestive heart disappointment, hypertension, age ≥ 75 y, diabetes mellitus, past stroke or transitory ischemic assault) score is 3. Her HAS-BLED (hypertension with a systolic blood weight >160 mm Hg, unusual renal or liver work, stroke [caused by a drain], dying, labile worldwide normalized proportion [INR], elderly [age > 65 y], drugs [ASA, nonsteroidal anti-inflammatory drugs (NSAIDs)] or liquor [≥8 drinks/wk]) score is 2, which is based on her age and ASA utilize. (This score does not take into consideration her other medicines that increment her chance of dying [ie, ticagrelor and paroxetine]). Mrs K.A. has an sign for an OAC for AF stroke anticipation; in any case, you choose allude to">to allude to her cardiologist, as she is as of now taking DAPT for her later ACS and coronary stents.

Bringing evidence to practice Triple treatment may well be endorsed for patients with concomitant AF and later ACS, as DAPT has been appeared to be predominant to an OAC for decreasing the hazard of stent thrombosis,6 but was second rate to an OAC for anticipating thrombotic occasions in patients with AF.7 The 2016 Canadian Cardiovascular Society (CCS) rules for the administration of AF suggest TT (81 mg/d of ASA, 75 mg/d of clopidogrel, and an OAC) [3] for 3 to 6 months in patients with AF who are 65 a long time of age and more seasoned, have a CHADS2 score of 1 or more, and have experienced PCI, taken after by clopidogrel furthermore an OAC for 6 to 9 months (12 months add up to) after the index event, and after that OAC monotherapy.1 In any case, typically a conditional suggestion based on low-quality evidence.1 In put of TT, a few cardiologists might select DAPT for patients with a CHADS2 score less than 2 or double treatment (ie, clopidogrel furthermore an OAC) in patients with a tall hazard of dying. few expansive randomized controlled trials (RCTs) assessing antithrombotic regimens for ACS or AF alone, the accessible prove for patients with concurrent ACS and AF is negligible, and is essentially based on observational thinks about and open-label RCTs (Table 1). Meta-analyses have endeavored to evaluate the beneft of TT compared with other antithrombotic regimens; in any case, comes about are uncertain owing to change within the extent of patients with ACS at pattern, need of detailing of patient-specifc hazard variables (ie, CHADS2 and HAS-BLED scores), different terms of TT, and destitute think about quality. On the other hand, the chance of dying with TT has been well quantifed. Compared with DAPT or double treatment, TT pairs the in general chance of dying and is related with a 5% to 15% rate of major dying at 1 year. Roughly 1 in 10 drains are fatal. Not shockingly, the rate of dying increments with expanding length of Two open-label RCTs2, the Ideal Antiplatelet and Anticoagulant Treatment in Patients with Verbal Anticoagulation and Coronary Stenting) trial


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compared warfarin additionally clopidogrel with TT (ASA, warfarin, and clopidogrel) in 573 patients who gotten a coronary stent (69% had AF).9 The PIONEER-AF-PCI (Open-label, Randomized, Controlled, Multicenter Consider Investigating Two Treatment Techniques of Rivaroxaban and a Doseadjusted Verbal Vitamin K Opponent Treatment Procedure in Subjects with Atrial Fibrillation Who Experience PCI) think about, conducted with 2124 patients with AF who experienced PCI, had 3 treatment arms: double treatment (lowdose rivaroxaban [15 mg/d] additionally clopidogrel) [4]; TT with exceptionally low-dose rivaroxaban (2.5 mg twice every day); and TT with warfarin.2 Not one or the other ponder was fueled to look at thrombotic occasions and hence contrasts in effcacy might not have been detected. Both trials explored any dying as the essential conclusion point and concluded that double treatment come about in less dying than TT.,*by dying requiring therapeutic consideration, and the distinction in rate of major dying was not measurably signifcant between groups.2 Assist, as it were roughly 25% to 50% of patients had ACS as their file event. Based on the WOEST think about, the CCS rules prescribe double treatment (clopidogrel furthermore OAC) for 12 months in patients with AF who experience elective PCI.1 Selection of anticoagulants for TT. Most of the constrained prove with respect to TT is for warfarin. The previously mentioned meta-analyses that evaluated TT as it were included vitamin K antagonists—these thinks about give the biggest body of prove (15 and 18 considers, N=7182 and N=17708, separately)[5], in spite of the fact that both are generally based on observational data. On the off chance that warfarin is utilized, consider an INR target of 2.0 to 2.5 and screen INR regularly (eg, each 2 weeks), in spite of the fact that this limit target can be diffcult to achieve [6]. The 2016 CCS AF rules propose, based on extrapolation of information from the critical ACS.1 Be that as it may, the clinical effcacy and security of DOACs in a TT regimen has not been built up. Of the DOACs, as it were rivaroxaban and dabigatran have randomized controlled security information compared with warfarin (as portion of TT) in patients with AF (Table 1).2,8-12,19 Be that as it may, these trials were not fueled to assess adequacy, and so have not built up a lessening in stroke and systemic embolism rates in AF. The PIONEER-AF-PCI consider compared 15 mg of rivaroxaban every day additionally 75 mg of clopidogrel every day, and 2.5 mg of rivaroxaban twice day by day furthermore DAPT (75 mg/d of clopidogrel furthermore 75 to 100 mg/d of ASA), with warfarin furthermore DAPT [7]. 2 In terms of security, both rivaroxaban methodologies come about in less clinically signifcant dying compared with warfarin (contrasts in major dying rates were not factually signifcant). 2 At the time of distribution, 2.5-mg tablets of rivaroxaban are not commercially accessible in Canada. There was constrained detail with respect to the term of TT in these patients. The expansion of DAPT to an OAC expanded major dying, but the outright chance was least with 110 mg of dabigatran twice daily. The other point of interest AF trials that compared DOACs with warfarin prohibited patients taking clopidogrel, and as it were roughly one-third of the patients were taking ASA. Three of the DOACs have been compared with fake treatment in TT regimens for auxiliary ACS anticipation (Table 1); be that as it may, the extent of patients with AF was not reported.10-12 The RCTs including dabigatran and apixaban fizzled to illustrate a beneft, but uncovered expanded major dying rates [8]. Selection of antiplatelets for TT. Clopidogrel is the favored antiplatelet to be utilized in combination with ASA and an OAC. The more up to date, more strong antiplatelet specialists, prasugrel and ticagrelor, are not suggested owing to an expanded hazard of dying compared with clopidogrel and constrained information on their part as portion of TT. In any case, on the off chance that clopidogrel isn't an alternative (eg, owing to sensitivity, stent thrombosis whereas accepting treatment), ticagrelor or prasugrel could be considered.



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**Table 1. Summary of RCTs**

| STUDY | POPULATION | INTERVENTION OR COMPARATOR | OUTCOMES | COMMENTS |
|---|---|---|---|---|
| **TT RCTs of patients who received a coronary stent** | | | | |
| PIONEER-AF-PCI,[2] 2016<br>• Open-label, randomized trial<br>• 26 countries (about 10% from North America)<br>• N = 2124 | • Nonvalvular AF and PCI with stent<br>• Mean age 70 y<br>• Elective PCI: 61.5%<br>• $CHA_2DS_2$-VASc score: 0–1, 9.5%; 2–4, 54.7%; 5–7, 35.9%<br>• HAS-BLED score: ≤ 2, 29.8%; 3–4, 65.8%; ≥ 5, 4.5% | • Group 1: 15 mg/d of rivaroxaban (10 mg/d if CrCl 30–50 mL/min) and $P2Y_{12}$ inhibitor for 12 mo<br>• Group 2: 2.5 mg of rivaroxaban twice daily and DAPT for 1, 6, or 12 mo; step down to rivaroxaban and ASA (75–100 mg/d) until 12 mo after stent<br>• Group 3: warfarin (INR 2.0–3.0) and DAPT for 1, 6, or 12 mo; step down to warfarin and ASA (75–100 mg/d) until 12 mo after stent<br>• $P2Y_{12}$ inhibitor: 94% clopidogrel<br>• Proportion of patients taking 10 mg/d of rivaroxaban not reported | • Primary end point of clinically significant bleeding (composite of TIMI major and minor bleeding, and bleeding requiring medical attention): group 1, 16.8%; group 2, 18%; group 3, 26.7%<br>• $P < .01$ for groups 1 and 2 vs group 3; NNT = 11 and NNT = 12, respectively, at 1 y<br>• CV event (CV death, MI, or stroke): no difference | • DAPT duration for groups 2 and 3 (non-randomized): 1 mo, 15.8%; 6 mo, 34.9%; 12 mo, 49.3%<br>• PPI use at baseline: 38%<br>• Not powered to assess CV outcomes<br>• Difference in major bleeding was not statistically significant between groups |
| ISAR-TRIPLE,[8] 2015<br>• Open-label, randomized trial<br>• Germany and Denmark<br>• N = 614 | • Indication for long-term OAC and need for PCI<br>• Mean age 73 y<br>• > 65% stable angina<br>• > 80% AF<br>• DES: 100%<br>• $CHADS_2$ score: 0–1, 17%–21%; 2–3, 61%–64%; 4–5, 13%–20%; > 5, 1%–2%<br>• $CHADS_2$ score ≥ 3: 6 wk (22.4%) vs 6 mo (14.5%) | • TT (75 mg/d of clopidogrel, 75–200 mg/d of ASA, and warfarin [INR 2.0–3.0]) for 6 wk vs 6 mo | • Primary end point (composite of death, MI, stent thrombosis, stroke, and TIMI major bleeding): no difference at 9 mo | • No significant differences in secondary end points between groups, including TIMI major bleeding<br>• No net clinical benefit between 6 mo vs 6 wk of TT |
| WOEST,[9] 2013<br>• Open-label, randomized trial<br>• Netherlands<br>• N = 571 | • Indication for long-term OAC and need for PCI<br>• Mean age 70 y<br>• 69% AF<br>• Only 27% had ACS at baseline<br>• 65% DES, 30% BMS | • Dual therapy (75 mg/d of clopidogrel and warfarin) for 12 mo vs TT (80–100 mg/d of ASA, 75 mg/d of clopidogrel, and warfarin) for 12 mo<br>• Target INR of 2.0–3.0 for both groups | • Primary end point (any bleeding at 1 y): 19.4% vs 44.4%, HR = 0.36, $P < .0001$, NNT = 4<br>• Secondary end point (composite of death, MI, stroke, target vessel revascularization, and stent thrombosis): 11.1% vs 17.6%, HR = 0.6, $P = .025$, NNT = 16, driven by reduction in death | • Duration<br>–BMS: 1 mo to 1 y<br>–DES: at least 1 y<br>• No significant difference in TIMI major bleeding<br>• Underpowered for ischemic events<br>• PPI use at baseline: about one-third |

*Duration of TT.* The term of TT is exceedingly individualized. The CCS rules suggest 3 to 6 months of treatment, but note the length is subordinate on seen dangers of coronary stent thrombosis and major dying, such as the patient's HAS-BLED score, sort of stent set (uncovered metal vs medicate eluting), and hazard variables for stent thrombosis (eg, diabetes mellitus, frst-generation drug-eluting stents, number of stents). Different lengths of TT have been assessed in RCTs. The ISAR-TRIPLE (Intracoronary Stenting and Antithrombotic Regimen-testing of a 6-week versus a 6-month Clopidogrel Treatment Regimen in Patients with Concomitant Ibuprofen and Verbal Anticoagulant Treatment Taking after Drug-eluting Stenting) consider compared 6 weeks with 6 months of TT and found no measurably signifcant contrast between the bunches for the essential composite conclusion point of passing, myocardial dead tissue, stent thrombosis, ischemic stroke, and major bleeding.8 Be that as it may, as it were one-third of the ponder populace had later Lessening the chance of dying. The HAS-BLED score may be a valuable device for surveying the chance of dying for patients with AF.1 Tending
to reversible chance variables is significant in decreasing dying hazard, particularly for patients


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taking TT. These chance variables incorporate uncontrolled blood weight, labile INR, utilize of medicines that incline the persistent to dying (eg, NSAIDs, corticosteroids, particular serotonin reuptake inhibitors), and visit liquor utilization (ie, ≥ 8 alcoholic drinks per week). Patients taking TT ought to have their dying hazard evaluated some time recently start and all through treatment. The expansion of a proton pump inhibitor (PPI) ought to be considered as gastroprotection for patients taking TT, especially for those with a history of gastrointestinal dying or ulcers. Whereas there's a need of information tending to the effcacy of gastroprotection [9] in TT, prove does appear that PPIs diminish the chance of upper gastrointestinal dying by at slightest 50% in patients taking DAPT.25 Already, concerns were raised with respect to a potential drug-drug interaction between PPIs and clopidogrel based on observational trial data.26 More later RCT information propose a clinically signifcant interaction is improbable. Be that as it may, on the off chance that starting a PPI in a quiet taking clopidogrel, consider selecting an operator other than omeprazole or esomeprazole owing to a lower hazard of sedate interaction.

Back to Mrs K.A. Mrs K.A.'s cardiologist would like to see her in his offce, but meanwhile , he inquires you to halt her ticagrelor and start 75 mg of clopidogrel day by day (beginning within the morning after her final evening dosage of ticagrelor) for 10 months (ie, she will get a P2Y12 inhibitor for a add up to of 12 months after coronary stent inclusion). She is to proceed taking her low-dose ASA for another month, at that point halt (ie, she will get ASA treatment for a add up to of 3 months after coronary stent addition). She is endorsed 3 mg of warfarin day by day, with a proposed INR target of 2.0 to 2.5 whereas taking TT [10]. You choose to start 40 mg of pantoprazole every day whereas Mrs L.F. is getting TT, conjointly choose to extend her metoprolol to 75 mg twice day by day to realize superior rate control. You reassess her paroxetine, as specific serotonin reuptake inhibitors can increment the hazard of gastrointestinal bleeding.

**Conclusion:** Questions stay with respect to the perfect antithrombotic regimen and treatment term for patients with AF who have ACS or who experienced PCI with coronary stenting. Adjusting the chance of thrombotic occasions and dying may be a restorative challenge. A cardiologist ought to be counseled some time recently starting and deciding the length of TT, with a clear arrange for step-down to a double or single-agent regimen once TT is total. As dying chance is aggregate, clear communication among wellbeing care suppliers, patients, and caregivers is imperative to encourage adherence to the prescribed length of TT. Moreover, tending to any reversible hazard variables for dying and considering gastroprotection are imperative steps to optimizing persistent security.

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