

An Observational Study of Rivaroxaban in Thrombotic Coronary Artery Disease

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Abstract: ***Introduction:** The pathogenesis of acute myocardial infarction (AMI) and unstable angina is the rupture of the coronary artery plaque resulting in acute thrombotic occlusion of a coronary artery. Thus, the thrombus forms an integral part of the atherosclerotic coronary plaques. There is a consensus that intracoronary thrombus makes up a challenging target for revascularization because of its unique characteristics. It has a crucial impact on the performance and outcome of the percutaneous coronary intervention (PCI). **Aims and objectives:** This study reviews the alternative management of coronary artery thrombus and highlights the role of the oral anticoagulation in its management **Materials and methods:** We took 60 patients of ACS who underwent CAG suggestive of thrombotic occlusion of coronary arteries. They were prescribed oral anticoagulation along with DAPT and statins and check angiography were done after 15 days. **Results:** Out of 60 patients, 24 (40%) patients shows complete regression of thrombotic lesions, 18 (30%) patients shows regression of lesions causing decreasing in thrombotic burden, while 16 (26.6%) patients shows no regression of lesion and 2 (3.4%) patients lost to follow up. **Conclusion:** Oral anticoagulation can be used in thrombotic coronary occlusion.*

Keywords: Thrombotic coronary artery disease, Rivaroxaban, Heparin, Coronary angiography, PCI.

1. Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide with a prevalence that has now reached pandemic levels as a consequence of the rapid modernization of the developing world. Its presentation as an acute coronary syndrome (ACS) is a frequent reason for hospital admission and of profound implications for personal, societal and global health. Patho-physiologically during an ACS, the rupture of a vulnerable plaque within the coronary artery represents the beginning of a complex inflammatory and coagulation cascade. The rupture of the necrotic and lipid enriched plaque core attracts activated macrophages releasing several inflammatory cytokines such as matrix - metallo - proteinases (MMPs) and initiates primary hemostasis [1]. On the other hand, due to endothelial damage, sub - endothelial tissue factor is released and initiates the extrinsic coagulation pathway. Consequently, specific coagulation factors are activated in a step - wise manner, such as factor X (Stuart - Prower factor) thereafter activating thrombin (factor IIa), which in turn leads to the formation of fibrin [2]. Arterial thrombi usually form in regions of disturbed flow and at sites of rupture of an atherosclerotic plaque, which exposes the thrombogenic sub endothelium to platelets and coagulation proteins; plaque rupture may also produce further narrowing due to hemorrhage into the plaque [3, 4, 5, 6, 7]. Nonocclusive thrombi may become incorporated into the vessel wall and can accelerate the growth of atherosclerotic plaques [8, 9, 10]. When flow is slow, the degree of stenosis is severe, or the thrombogenic stimulus is intense, the thrombi may become totally occlusive. Arterial thrombi usually occur in association with preexisting vascular disease, most commonly atherosclerosis; they produce clinical tissue ischemia either by obstructing flow or by embolism into the distal microcirculation. Activation both of blood coagulation

and of platelets is important in the pathogenesis of arterial thrombosis. These 2 fundamental mechanisms of thrombogenesis are closely linked in vivo, because thrombin, a key clotting enzyme generated by blood coagulation, is a potent platelet activator, and activated platelets augment the coagulation process. Therefore, both anticoagulants and drugs that suppress platelet function are potentially effective in the prevention and treatment of arterial thrombosis, and evidence from results of clinical trials indicates that both classes of drugs are effective. These different mechanisms alleviate the formation of an intracoronary thrombus, which represents the final step leading to an acute coronary ischemia [11]. The associated clinically relevant adverse outcomes are potentially life - threatening and might consist in (cardiovascular) death, myocardial re - infarction or thrombo - embolic cerebral stroke. Several studies demonstrated beneficial effects of treating patients either suffering from SCAD or ACS with anti - platelet agents either within a mono or dual anti - platelet therapy (DAPT) regimen. These anti - platelet agents such as acetyl - salicyl - acid (ASA), thienopyridines (clopidogrel or ticlopidine), or new P2Y₁₂ inhibitors (new thienopyridines) were shown to reduce the incidence of re - current cardiovascular events, such as cardiovascular death, myocardial infarction or stroke in these patients [11, 12]. Moreover, periprocedural intravenous anticoagulation is recommended by additional use of intravenous unfractionated heparin or glycopeptide IIb/IIIa (GP IIb/IIIa) inhibitors during PCI [11]. Additional ongoing oral anticoagulation besides antiplatelet therapy in patients with SCAD after ACS or PCI is still under debate. For instance, additional treatment with vitamin k antagonists (e. g., warfarin) (VKA) on top to ASA treatment or even alone was demonstrated as being more effective in preventing the above - mentioned cardiovascular events compared to ASA drug therapy alone. Such data increasingly encouraged the

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concept of an additional therapy with oral anticoagulants besides anti - platelet agents in patients with CAD. Anticoagulation is important in the management of cardiovascular disorders; however, traditional anticoagulants such as heparins and vitamin K antagonists (VKAs) have limitations, including parenteral administration with the former and the need for coagulation monitoring and dose adjustments with the latter. Heparin and PCI is an established mode of treatment for intra coronary thrombotic lesions in coronary angiography. Treatment for coronary artery thrombus involves medications and revascularization to improve myocardial perfusion. PCI has its own complication in thrombotic lesions. Percutaneous devices such as aspiration catheter and embolic protector decrease distal embolization and improve myocardial blood flow and clinical outcomes [13, 14]. Aspiration catheter manual target to lessen thrombus burden while the embolic protector target to catch the debris release during PCI. Manual thrombus aspiration of the infarct - related vessel is a useful method for the rapid decrease in the thrombotic burden, preventing the distal embolization of thrombus, preserving the microvascular integrity, and reducing infarct size. Manual thrombectomy, therefore, improves myocardial perfusion grade. TAPAS trial showed a mortality reduction, which led the guidelines to recommend routine manual aspiration [15]. However, the latest trials have shown no clear - cut benefit of routine manual aspiration in acute myocardial infarction [16, 17]. Increased thrombus burden may influence stent opposition, which can lead to low TIMI flow and poor outcomes. The best method of primary percutaneous intervention in the setting of coronary thrombus has been reported in the SINCERE database [18]. According to it, if the thrombus size is small, direct stenting may be adequate. If the thrombus burden is more, it is wise to perform aspiration thrombectomy before stenting to minimize distal embolization and no - reflow. If the thrombus burden is vast, then more aggressive thrombectomy devices such as Angio jet Rt are better to remove thrombus. There is a consensus that intracoronary thrombus makes up a challenging target for revascularization because of its unique characteristics. It has a crucial impact on the performance and outcome of the percutaneous coronary intervention (PCI). So, PCI also has its own complications in thrombotic coronary lesion & need more expertise which also increases the economic burden in poor resource countries like India.

The mainstay pharmacologic therapy for managing thrombus- containing lesions includes aspirin, thienopyridines (clopidogrel, prasugrel, ticagrelor), and unfractionated heparin [19, 20]. But in the case of persistent thrombus, drugs such as GP IIb/IIIa inhibitors and vasodilators can help to improve epicardial and myocardial blood flow [21, 22]. Heparin needed to be given as a parenteral administration which increases hospital stay duration & it leads to more economic burden to the patients which is more bothersome in developing countries like India where health insurance is available only with few patients. We conducted an observational study in our institute GMC & SSH Nagpur that thrombotic coronary artery lesion patients who are not willing/not affordable for parenteral heparin/subcutaneous LMWH and PCI, we offered them NOAC - Rivaroxaban as home - based treatment and check CAG was done after 15 days & lesion was reassessed.

Aims & Objectives

- 1) Efficacy of NOAC– Rivaroxaban in thrombotic coronary artery disease.
- 2) Find alternative pharmacological regimen (other than heparin) for thrombotic coronary artery disease.

2. Methodology

An observational study was performed at Govt Medical College & Super Specialty Hospital Nagpur. We had 60 patients of ACS (STEMI, NSTEMI, UA) during the period of 1&1/2 year duration dated 01 - 03 - 2021 to 01 - 09 - 2022 who were enrolled for study based on the inclusion and exclusion criteria.

Inclusion criteria:

- 1) Acute coronary artery syndrome patients.
- 2) Patients having thrombus/thrombotic lesion in their Coronary artery angiography.
- 3) Patients not willing for parenteral heparin / percutaneous coronary angioplasty.
- 4) Patients ready to take oral anticoagulant rivaroxaban along with conventional drugs like DAPT, Statins etc after explaining that it is not an established treatment regimen for thrombotic coronary artery disease.

Exclusion criteria:

- 1) Patients not having thrombotic lesion in coronary angiography.
- 2) Patients willing either for heparin (parenteral/subcutaneous) or for PCI.
- 3) Patients not willing to take oral anticoagulation in form of rivaroxaban.
- 4) Patients having contra - indication for Rivaroxaban.

After meeting stringent inclusion and exclusion criteria all the 60 patients were enrolled during above mentioned time period for the study. rivaroxaban 15 mg once a day was given to the patients and check CAG was done after mean duration of 15 days. Patients were telephonically followed in the meantime and on having chest pain were advised to go for Cath immediately. Patients having persistent lesions >70% luminal area involvement by visual assessment were advised to go for PCI. Patients with regressed lesion to <70 % were advised for Guideline directed medical treatment.

Quantification of coronary thrombi based on coronary angiography -

Angiography is commonly used for quantification of the thrombus burden. Angiographically, intracoronary thrombus is defined as the presence of a filling defect with reduced contrast density or haziness. Most widely used TIMI scale (Table 1) relies on the relative estimated size of the thrombus and of the affected vessel, using a score ranging from grade 0 (no thrombus), to grade 5 (very large thrombus with complete occlusion).

Table 1: TIMI (Thrombolysis in Myocardial Infarction) thrombus scale

Grade	Description
0	No angiographic evidence of thrombus
1.	Possible thrombus: decreased contrast density or haziness, irregular lesion contour, a smooth convex meniscus at the site of a total occlusion suggestive, but not firmly diagnostic of thrombus
2.	Definite thrombus presents in multiple angiographic Defined by marked irregular lesion contour with a filling defect Greatest dimension of thrombus is < 1/2 vessel diameter
3.	Definite thrombus appears in multiple angiographic views with greatest dimension from >1/2 to <2 vessel diameters
4.	Definite large size thrombus present with greatest dimension >2 vessel diameters
5.	Complete thrombotic occlusion of a vessel

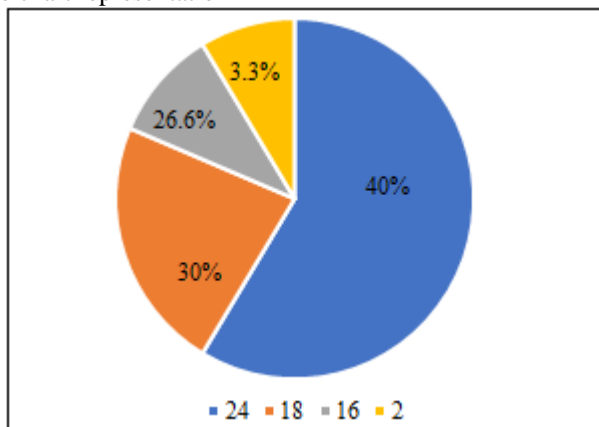
Results - 60 patients were selected fulfilling inclusion and exclusion criteria, baseline characteristics are discussed below

Distribution of patient’s pre and post rivaroxaban (15 days) therapy, CAG lesions (Table 2) -

Table 2: Distribution of patients pre and post rivaroxaban therapy, CAG lesions

Baseline CAG	Post rivaroxaban CAG	No of patients
Thrombus obstructing the coronary artery >70%	Thrombus obstructing the coronary artery <70%	24
	Thrombus obstructing the coronary artery decrease by 1 or 2 grade but still >70%	18
	Thrombus remained same by grade and obstructing coronary artery >70%	16
	Lost to follow - up	2
	Total- 60	

Pie chart representation -



Pie chart 1. showing that 40% patients with resolved lesions, 30% patients with reduced lesion by grade 1 or 2, 26.6 % patients whose thrombus remained the same & 3.3% patients lost to follow up.

Table 3: Distribution of the patients on the basis of type of ACS -

Diagnosis	No of Patients
IHD - AWTMI	51
IHD - IWMI	6
IHD - UA	3
IHD - NSTEMI	0

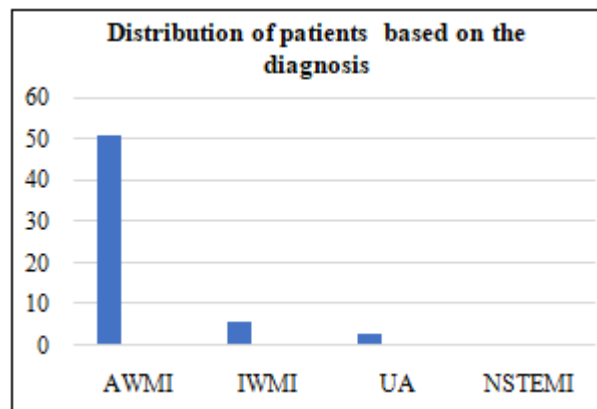
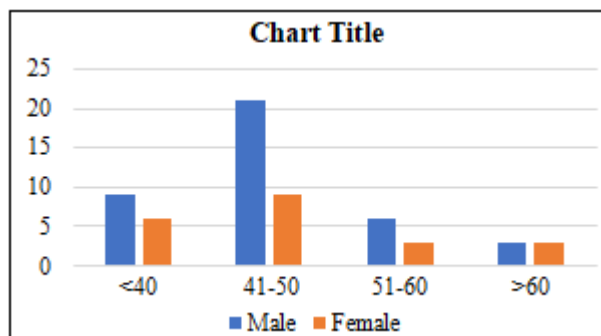


Table 4: Distribution of the patients on the basis of Age & Sex

Age group	Male	Female	Total =60
<40	9	6	15 (25%)
41 - 50	21	9	30 (50%)
51 - 60	6	3	9 (15%)
>60	3	3	6 (10%)



Discussion: Though this is a non - randomized, observational study and only 60 patients of ACS were taken meeting inclusion and exclusion criteria.

Effect on Coronary artery thrombotic lesion –

60 patients whose CAG showed thrombotic coronary lesion & obstructing the lumen >70% who were not ready to go for PCI, In the selected 1 and half year duration, were prescribed oral Rivaroxaban 20 mg daily for 15 days and were called for follow up CAG at 15th day. On follow up CAG, 40% patients lesion regressed to <70% and they were not prescribed PCI, hence they were managed medically. Around 30% of patients lesion was regressed by grade 1 or 2 according to above given TIMI thrombus scale & most of them were prescribed for PCI. In around 26.6% patients the CAG lesion remained the same and all of them were prescribed for PCI. 2 patients (3.3%) were lost to follow up. It denotes that mechanism of ACS is atherothrombotic and oral NOACS may be given in patients of thrombotic coronary artery disease instead of heparin, which is more convenient to administer and have less risk of bleeding.

Distribution of patients as per type of ACS –

Most of the patients who showed thrombotic coronary lesion were STEMI patients (100 %) of them 85% were of AWMI, 10 % were of IWMI, 5 % were of UA. So, it proves that most of ACS are due to atherothrombotic lesion due to multiple reasons like plaque rupture and erosion etc & giving anticoagulation will be helpful.

Distribution of patients as per age –

In this study maximum number of patients were in age group of 41 - 50 years 50% followed by <40years 25%. Most of ACS patients having thrombotic coronary lesion are young and they don't prefer to remain in hospital, so giving oral NOACS may be apt strategy for them.

3. Conclusion

Major learning points from this observational study are –

- 1) As most ACS are due to atherothrombotic lesion & for primary PTCA/PAMI, relative expertise & special instruments needed in this situation are not available in many parts of our country in major cities also opting for conservative management in many times is a choice.
- 2) While opting for conservative management in hospital admission and giving IV Heparin is very cumbersome for patients and it also increases the cost burden to the patients as most of our patients are not having health insurance.
- 3) Using oral Vitamin k antagonists needs INR monitoring and frequent follow up, which is not feasible always.
- 4) NOACS are very efficacious, available in oral form, no need of PT - INR monitoring neither admission and frequent follow up, so seems best option at present specially for poor resource countries.
- 5) A randomized study is suggested with NOACS/Rivaroxaban effectiveness against IV heparin and Primary PTCA to test NOACS effectiveness, pros & cons.

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