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RESEARCH ARTICLE

OBSERVATIONAL STUDY TO COMPARE THE OUTCOMES OF APIXABAN PLUS ASPIRIN VERSUS DUAL ANTIPLATELET THERAPY AFTER REVASCULARIZATION IN CHRONIC LIMB THREATENING ISCHEMIA PATIENTS

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Key words:-
Chronic Limb Threatening Ischemia (CLTI), Peripheral Arterial Disease (PAD)

Abstract

Introduction: Patients with peripheral artery disease requiring lower extremity revascularization are at high risk of major adverse limb and cardiovascular events. Primary patency rate of above knee femoropopliteal reversed saphenous vein graft at 1 and 4 year is 99 and 69% and for below knee femoropopliteal reversed saphenous vein graft at 1 and 4 year is 98 and 77% respectively.

Need for the Study: Antiplatelets and oral anticoagulants has been well recognized cardiac and cerebral protective effects and may also improve early graft patency. Considering the safety profile of apixaban3 over other newer oral anticoagulants and since only limited studies are available comparing the newer oral anticoagulant apixaban plus aspirin and dual antiplatelet therapy in Indian population, this study is proposed.

Methods: The study population includes 306 patients with age 50 years or more males or females who have a documented PAD with CLTI undergoing limb revascularization either open surgery or endovascular or hybrid approach in Thanjavur medical college from May 2019 to June 2023. Postoperatively patients were discharged wth either apixaban plus aspirin therapy or dual antiplatelet therapy. Patients were excluded if they were clinically unstable, were at heightened bleeding risk. The primary outcome studied include major adverse limb events and major reintervention rate. The secondary outcomes studied include major adverse cardiovascular events, stroke, re- and cross-over intervention rates,major and non major bleeding for a period of 5 years.

Results: Interim results of 77 patients who fulfil the inclusion criteria are analysed for publication.The primary outcome – major amputation above knee level occurred in 6.4% of apixaban /aspirin group and and 5.7% of aspirin/clopidogrel group and major re intervention occurred in 12.9% of apixaban /aspirin group and and 17.1% of aspirin/clopidogrel group . Secondary outcomes-major adverse cardiovascular events occurred in 5.5% of apixaban /aspirin group and and 4.8% of aspirin/clopidogrel group . Re and crossover intervention occurred in 6.4% of apixaban /aspirin group and and 8.5% of aspirin/clopidogrel group (p value of 0.5). non major bleeding occurred in 3.2% of apixaban /aspirin group and and 20% of aspirin/clopidogrel group (p value of 0.038).

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Conclusion: From this study we found that - there is no significant difference with respect to MALE, MACE in CLTI patients undergoing Infra inguinal revascularization between Apixaban + Aspirin and Aspirin + Clopidogrel groups except for non major bleeding. With inclusion of all patients enrolled from 2019 till 2023 and after completion of 4 years follow up we try to overcome these limitations noted in this interim study.

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Introduction:-

CLTI was defined as persistent, recurring ischemic rest pain requiring opiate analgesia for at least 2 weeks and ankle systolic pressure lower than 50mm Hg or toe systolic pressure lower than 30mm Hg; or ulceration or gangrene of the foot or toes and ankle systolic pressure lower than 50mm Hg; or toe systolic pressure lower than 30mm Hg or absent pedal pulses in diabetics.[1]CLTI Patients require Revascularization (Either open or endovascular or Hybrid procedure). Open Procedures for Infra Inguinal Revascularization includes Bypass with autogenous Vein graft or synthetic graft. The Primary patency rate of Infrainguinal bypass with vein graft at 4 year is in the range of 69% to 77%[2].

Patency in percentage after**above knee** femoropopliteal bypass[3]

Graft Type	1-Month	6-Month	1-Year	2-Year	3-Year	4-Year
Reversed saphenous vein	99	91	84	82	73	69
Arm vein	99	-	82	65	60	60
Human umbilical vein	95	90	82	82	70	70
Polytetrafluoroethylene	-	89	79	74	66	60

Patency of **Below-Knee** Femoropopliteal Grafts[4]

Graft Type	1-Month	6-Month	1-Year	2-Year	3-Year	4-Year
Reversed saphenous vein	98	90	84	79	78	77
In situ vein bypass	95	87	80	76	73	68

Endovascular Options include angioplasty and Stenting.

Antiplatelet and Antithrombotic therapy after Revascularization:

Patients undergoing revascularization require antiplatelet therapy post operatively.

VOYAGER-PAD trial compared the effects of low-dose rivaroxaban in PAD patients who underwent peripheral revascularization. In this trial, over 6500 patients were randomized to receive either low-dose rivaroxaban (2.5mg twice daily) plus aspirin (100mg daily) versus aspirin alone. Results showed that patients on low-dose rivaroxaban were less likely to experience the primary outcome -acute limb ischemia, major amputation for vascular cause, myocardial infarction, ischemic stroke or death from cardiovascular cause (17.3% vs. 19.9% aspirin alone; P = 0.009) as well as need for unplanned revascularization for recurrent ischemia (HR 0.88, CI 0.79–0.99; P = 0.03) over the subsequent 3 years after randomization and there was no statistically significant difference in outcomes depending on type of intervention[5].

ESVS antithrombotic guidelines (2023)[6]:

Patients not at high risk of bleeding & undergoing an **endovascular** intervention for lower extremity PAD should be considered for

1. Should be considered for Post-procedural Aspirin (75 mg or 100 mg once/day) and Rivaroxaban (2.5 mg twice/day) **(Class IIa level B) or**
2. May be considered for Post-procedural DAPT (Aspirin 75 mg and Clopidogrel 75 mg) for no more than six months **(Class IIb level C)**

Patients not at high risk of bleeding& undergoing an **Endarterectomy/ Bypass with autologous vein/ synthetic graft** for lower extremity PAD should be considered for Should be considered for Post-procedural Aspirin (75 mg or 100 mg once/day) Rivaroxaban (2.5 mg twice/day) **(Class IIa level B)**

The role of aspirin and low dose rivaroxaban in preventing major adverse limb and cardiac events has been well established. However there is paucity of literature on the role of other newer oral anticoagulants in combination with Aspirin with regard to prevention of major adverse limb and cardiac events.

Ghadeer K Dawwa in their study compared apixaban with rivaroxaban in patients Venous Thromboembolism and found that apixaban had lower rates of bleeding than users of rivaroxaban[7].

AT Cohen et al[8] compared all newer oral anticoagulants for treatment of VTE and found that reductions in major or Clinically Relevant Non Major bleed for initial/long-term treatment were significantly better with apixaban compared with all other NOACs. Also apixaban has a renal clearance of only 27% compared to 33% with Rivaroxaban.

Considering the better safety profile and lower renal clearance of apixaban over rivaroxaban, apixaban has been chosen over rivaroxaban for patients undergoing revascularization in our study.

Methodology:-

From 2019 all the patients aged 50 years and above who underwent Infrainguinal revascularization for CLTI at department of vascular surgery were assessed for bleeding risk (HAS- BLED score) and patients without heightened bleeding risk (</=2) were started on either apixaban 2.5 mg twice daily plus aspirin 75 mg once daily or aspirin 75 mg plus clopidogrel 75 mg once daily for one year and patients with heightened bleeding risk (HAS-BLED score > 2) were discharged with Aspirin alone.

HAS – BLED Score:[9]

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

To calculate HAS- BLED Score:

1. **Hypertension** is defined as systolic blood pressure >160 mmHg.
2. **Abnormal renal function** is defined as the presence of chronic dialysis, renal transplantation, or serum creatinine ≥200 micromol/L.
3. **Abnormal liver function** is defined as chronic hepatic disease (eg, cirrhosis) or biochemical evidence of significant hepatic derangement (eg, bilirubin more than 2 times the upper limit of normal, plus 1 or more of aspartate transaminase, alanine transaminase, and/or alkaline phosphatase more than 3 times the upper limit of normal).

4. **Bleeding predisposition** includes chronic bleeding disorder or previous bleeding requiring hospitalization or transfusion.
5. **Labile INRs** for a patient on warfarin include unstable INRs, excessively high INRs, or <60% time in therapeutic range.

This is a retrospective observational study being including patients who underwent revascularization for CLTI from May 2019 to June 2023 with 4 years follow-up thereafter. The interim results of the patients who underwent procedure during that period and had completed 4 years of follow up are analyzed. Data of patients (clinical history and examination findings, pre-op investigations, surgical procedure, intra-op and post op events, Serial ABI values, Duplex examination (first study within 4 weeks of surgery, every 3 months for 1 year, every 6 months for next 2 years, and annually thereafter), post op wound status and details about additional surgeries has been collected from clinical records and telephonic calls with the patient.

Inclusion criteria
1.Age >/= 50 years, who underwent Infrainguinal revascularization
2. Patients **without** heightened bleeding risk (HAS BLED score of </= 2)

Exclusion criteria
1. Proven COVID 19 positive patients (Either CT chest / RT PCR)
2. Patients already on anticoagulation for other reasons.

All patients satisfying the above inclusion and exclusion criteria were included in the study.
The **Primary end points** of the study are:
a) Major Amputation - Above-ankle level amputation of the index limb
b) Major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis)
The **Secondary outcomes** studied were
1. Major adverse cardiovascular events(MACE),
2. Stroke,
3. Re intervention rates,
4. Major Bleeding - defined as fatal bleeding requiring a transfusion of ≥2 units of whole blood or red cells, or hemorrhage into a critical area or organ [eg, intracranial, intraocular, pericardial], or an overt bleed causing a fall in hemoglobin level of ≥2 g/dL).
5. Death due to Myocardial infarction.

Statistical analysis
Data are given as mean, standard deviation and Interquartile range for continuous data and as frequency for categorical data. Inferential data was assessed by univariate and multivariate regression analysis. Results from the regression analysis are expressed as p-value and odds ratio (OR) with a 95% confidence interval (CI).A p-value of less than 5% was considered significant. Data was analyzed using latest SPSS 23.0.0.2 version

Results:-

Total number of 306 CLTI patients who underwent revascularization of infrainguinal arterial occlusive disease from 2019 to 2023 are included in the study.Of these, patients satisfying the inclusion criteria were 77.Among them 36(46.7%) patients were getting apixaban plus aspirin with 34 males and 2 females. 41(53.2%) patients were getting aspirin and clopidogrel with 37 males and 4 females.Details of the comorbidities are as depicted in the table below.

Demographics & Clinical details

Aspirin + Apixaban Group	**(M =34, F =2)**
Aspirin + Clopidogrel Group	**(M =37, F =4)**

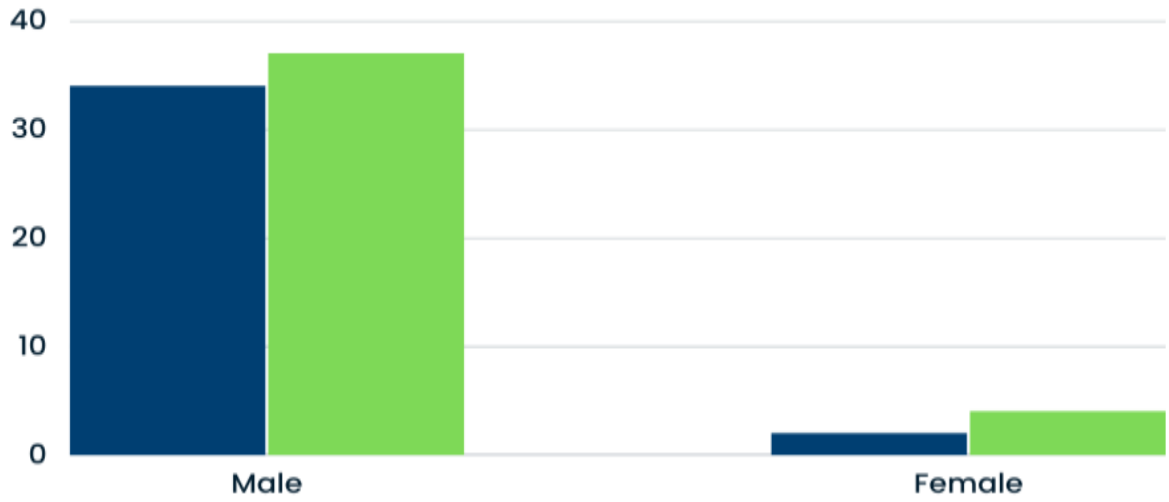

Fig. 1:- Demographics.

Comorbidities	APIXABAN PLUS ASPIRIN GROUP	ASPIRIN PLUS CLOPIDOGREL GROUP
1. DM	16	18
2. HTN	14	20
3. Pulmonary (COPD, BA,TB)	3	4
4. CAD	15	12
5. CVA	10	5

Table 1:- Comorbidities distribution.

WIfI Stage	Apixaban + Aspirin (n =36)
Stage 2	6 (16.6%)
Stage 3	9 (25%)
Stage 4	21 (58.3%)

Table 2:- WIfI Stage in Apixaban + Aspirin Group.

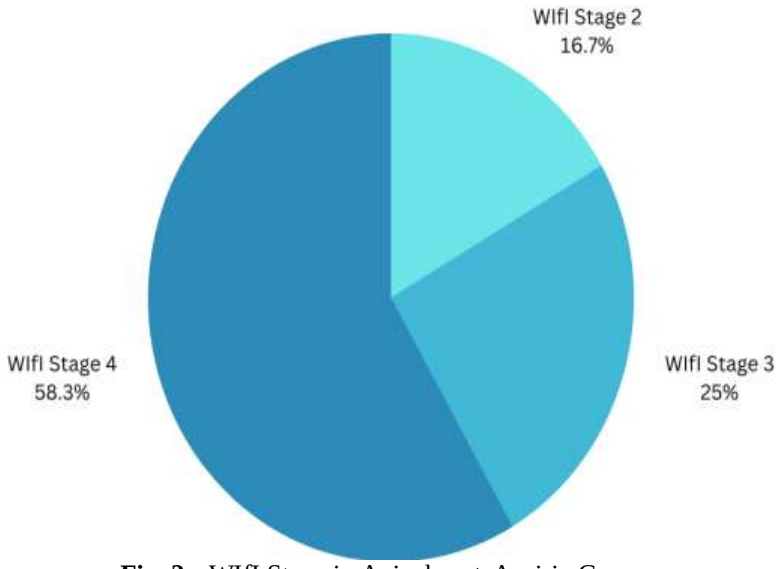

Fig. 2:- WIfI Stage in Apixaban + Aspirin Group.

WIfI Stage	Aspirin + Clopidogrel (n= 41)
Stage 2	8 (19.5%)
Stage 3	12 (29.2%)
Stage 4	21 (51.2%)

Table 3:- WIfI Stage in Clopidogrel + Aspirin Group.

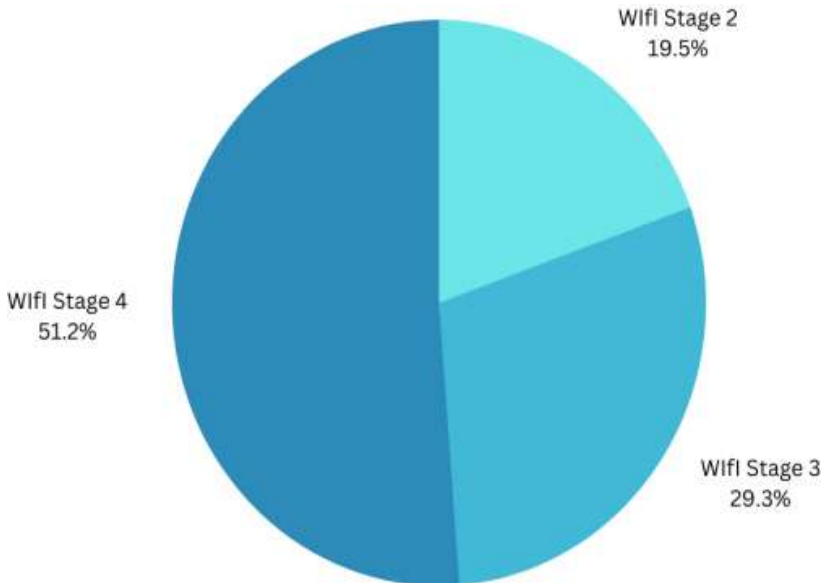

Fig.3:- WIfI Stage in Clopidogrel + Aspirin Group.

Outcomes

Primary Outcome- MALE	Apixaban + Aspirin (n =31) excluding 5 deaths	Aspirin + Clopidogrel (n= 35) excluding 6 deaths	P Value
Major amputation	**2 (6.4%)**	**2 (5.7%)**	**p = 0.9058**
Major Re-intervention	**4 (12.9%)**	**6 (17.1%)**	**p = 0.6372**

Table 4:- Primary outcomes.

In our study 6.4% of patients in Aspirin and Apixaban group underwent Major amputation compared to 5.7% in Aspirin + clopidogrel group, the difference was statistically insignificant (p=0.9058)whereas 12.9 % of patients in Aspirin and Apixaban group underwent Major Re intervention compared to 17.1% in Aspirin + clopidogrel group, the difference was statistically insignificant (p=0.66372).

Secondary Outcome – MACE	Apixaban + Aspirin (n =36)	Aspirin + Clopidogrel (n= 41)	P Value
Stroke	Nil	Nil	
Death from cardiovascular causes (MI)	2 (5.5 %)	2 (4.8 %)	p = 0.8902
Mortality			
Death from Other causes	3 (8.3%)	4 (9.7%)	
Total Deaths	5 (13.8%)	6 (14.6 %)	

Table 5:- Secondary outcomes.

In our study none of the patients had stroke, while 5.5 % of patients in Aspirin and Apixaban group died from cardiovascular causes compared to 4.8 % in Aspirin + clopidogrel group, the difference was statistically insignificant (p=0.8902).

In our study 6.4% of patients in Aspirin and Apixaban group had Re & cross over interventioncompared to 8.5 % in Aspirin + clopidogrel group, the difference was statistically insignificant (p=0.9058).while no reports of major bleeding was recorded, one in Aspirin and Apixaban group developed epistaxis and 7 in Aspirin + clopidogrel group developed non major bleeding episodes.

Secondary Outcome	Apixaban + Aspirin (n =31)	Aspirin + Clopidogrel (n= 35)	P Value
Re & Cross over intervention	2 (6.4%)	3 (8.5%)	p = 0.9058
Major Bleeding	Nil	Nil	

Non Major bleeding	1 (3.2%)	7 (20%)	**p = 0.0383**

Table 6:- Secondary outcomes contd.

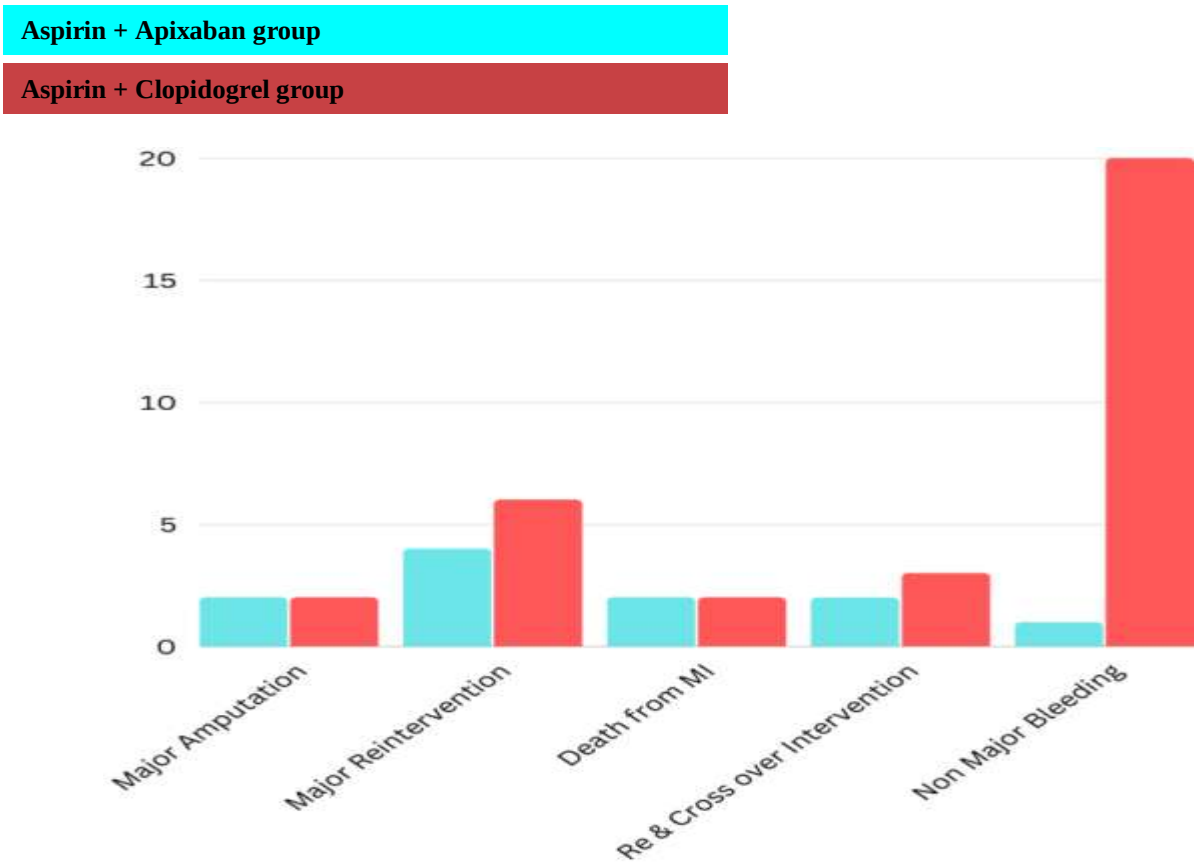

Fig. 4:- Primary & Secondary Outcomes.

Discussion:-

PAD is an important indirect marker for systemic atherosclerosis. PAD patients are at significantly increased risk for premature cardiovascular events, including myocardial infarction (MI), stroke, and death[10].25% of CLTI patients die of cardiovascular complications within 1 year of presentation.As reported by the Society for Vascular Surgery-Major adverse limb event (MALE) includes Above-ankle amputation of the index limb or major reintervention (new bypass graft, jump/interposition graft revision, or thrombectomy/thrombolysis) with an event rate of 6.1%, Major adverse cardiovascular event (MACE) includes Myocardial infarction, stroke, or death (any cause) with an event rate of 6.2%.[11]

All patients undergoing lower extremity revascularization needs antiplatelet therapy and anticoagulant therapy to prevent MACE,MALE, to improve graft patency. Several studies suggest the use of dual antiplatelet therapy even with no difference in risk of bleeding compared to aspirin monotherapy. Also results with use of vitamin K antagonists were not satisfactory as maintaining correct anticoagulation effect was difficult which is not an issue withnewer oral anticoagulants. several studies support the use of newer oral anticoagulants along with antiplatelet therapy.

The main finding of VOYAGER trial was that treatment with aspirin and rivaroxaban improved the primary composite efficacy outcome compared with aspirin single therapy during a median follow up of 28 months.[5] COMPASS Trail concluded that among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes than those assigned to aspirin alone.[12]

Outcome	VOYAGER Study	Aspirin + Apixaban	Aspirin + Clopidogrel
Major Amputation	5.8%	6.4%	5.7%
Reintervention	13.7%	12.9%	17.1%
Death from cardiovascular causes	5.7%	5.5%	4.8%

Table 7:- Comparison of results.

In our study 6.4% of patients in Aspirin and Apixaban group underwent Major amputation compared to 5.7% in Aspirin + clopidogrel group, with statistically insignificant difference (p=0.9058)whereas 12.9 % of patients in Aspirin and Apixaban group underwent Major Re intervention compared to 17.1% in Aspirin + clopidogrel group, the difference was statistically insignificant (p=0.66372). In our study none of the patients had stroke, while 5.5 % of patients in Aspirin and Apixaban group died from cardiovascular causes compared to 4.8 % in Aspirin + clopidogrel group, the difference was statistically insignificant (p=0.8902). 6.4% of patients in Aspirin and Apixaban group had Re & cross over intervention compared to 8.5 % in Aspirin + clopidogrel group (p=0.9058).while no reports of major bleeding was recorded, one in Aspirin and Apixaban group developed epistaxis and 7 in Aspirin + clopidogrel group developed non major bleeding episodes.These results were comparable to VOYAGER trial where major amputation was done in 5.8%, 13.7% underwent Re intervention and 5.7% died from cardiovascular causes.

One small multicentre double blind RCT (n = 203) compared Aspirin plus edoxaban with aspirin plus clopidogrel for three months following endovascular intervention. And found that after six months there was no difference in the re-stenosis and re-occlusion rate (RR 0.89; 95% CI 0.59 - 1.34). and there was no statistically significant difference in major bleeding rates between the groups[13]. In our study also no significant difference was found between major amputation, major re intervention and Death from cardiovascular causes.

Our study noted that Non major bleeding rate was 3.2% with Apixaban plus Aspirin group and 20% with Aspirin plus Clopidogrel group with significant p value of 0.038.

Limitations:
Limitations of our study includes Small group of study population and Outcomes with respect to open surgery and endovascular procedures were not studied.

Conclusion:-

From this study we found that - there is no significant difference with respect to MALE, MACE in CLTI patients undergoing Infra inguinal revascularization between Apixaban + Aspirin and Aspirin + Clopidogrel groups except for non major bleeding. With inclusion of all patients enrolled from 2019 till 2023 and after completion of 4 years follow up we try to overcome these limitations noted in this interim study.

References:-

1. Conte MS, Bradbury AW, Kolh P, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. J Vasc Surg. 2019;69. 3S–125S.
2. Aries PL, Arora S, Pomposelli Jr FB, et al. The use of arm vein in lowerextremity revascularizations: results of 520 procedures performed in eight years. J Vasc Surg. 2000;31:50–59.
3. Mills JL, Fujitani RM, Taylor SM. The characteristics and anatomic distribution of lesions that cause reversed vein graft failure: a five-year prospective study. J Vasc Surg. 1993;17:195–206.
4. Watelet J, Soury P, Menard JF, et al. Femoropopliteal bypass: in situ or reversed vein grafts Ten-year results of a randomized prospective study. Ann Vasc Surg. 1997;11:510–519.
5. Hiatt WR,et al.. Rivaroxaban and Aspirin in Peripheral Artery Disease Lower Extremity Revascularization: Impact of Concomitant Clopidogrel on Efficacy and Safety. Circulation. 2020 Dec 8;142(23):2219-2230.
6. C.P. Twine et al. European Society for Vascular Surgery (ESVS) 2023 Clinical Practice Guidelines on Antithrombotic Therapy for Vascular Diseases. Clinical practice guideline document. volume 78, issue 1, p260, july 2023.

7. Damon Houghton, et al. Apixaban Versus Rivaroxaban: Which One to Use in VTE Treatment?The Hematologist (2019) 16 (3).
8. Cohen AT, et al. Comparison of the Novel Oral Anticoagulants Apixaban, Dabigatran, Edoxaban, and Rivaroxaban in the Initial and Long-Term Treatment and Prevention of Venous Thromboembolism: Systematic Review and Network Meta-Analysis. PLoS One. **2015** Dec 30;10(12):e0144856.
9. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess one year risk of major bleeding in atrial fibrillation patients: The Euro Heart Survey. **Chest** 2010;138:1093-100.
10. Norgren L, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg. 2007;45(suppl S):S5–S67.
11. Reichle FA, et al. Infrapopliteal arterial reconstruction in the severely ischemic lower extremity. A comparison of long-term results of peroneal and tibial bypasses. Ann Surg. 1980;191 :59–65.
12. Jan Steffelet al. Net Clinical Benefit of Low-Dose Rivaroxaban Plus Aspirin as Compared With Aspirin in Patients With Chronic Vascular Disease. 21 May 2020 Circulation. 2020;142:40–48.
13. Edoxaban Plus Aspirin vs Dual Antiplatelet Therapy in Endovascular Treatment of Patients With Peripheral Artery Disease: Results of the ePAD Trial. J Endovasc Ther. 2018 Apr;25(2):158-168.