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# Comparative Efficacy of Apixaban, Dabigatran, Clopidogrel, and Aspirin Against Ferric-Chloride-Induced Thrombosis in the Carotid Arteries of Rats

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**Abstract:** Carotid injury induced by ferric chloride ($FeCl_3$) is a model of arterial thrombosis for evaluating antithrombotic medications. Preclinical comparisons of different drug classes are scarce. This study compared the efficacy and safety of two direct oral anticoagulants (DOACs)—apixaban and dabigatran—and two antiplatelet agents—clopidogrel and aspirin. Adult male rats were randomly assigned to control, $FeCl_3$, and $FeCl_3$ with apixaban, dabigatran, clopidogrel, and aspirin. The endpoints were thrombus weight, occlusion time (OT), bleeding time (BT), capillary-tube clotting time (CT), and blood count. In addition, serum thromboxane $B_2$ ($TXB_2$), D-dimer, malondialdehyde (MDA) and histopathological examination of the carotid artery were investigated. Compared to the controls, $FeCl_3$ caused a rapid, platelet-rich occlusion with increases in thrombus weight (7.18 mg), D-dimer (708.7 ng/mL), $TXB_2$ (549.7 pg/mL), and MDA (6.76 µmol/L). All treatments significantly prolonged OT compared with the $FeCl_3$ group. The DOACs (dabigatran and apixaban) demonstrated superior overall efficacy, prolonging OT and CT, reducing thrombus weight (2.53–3.97 mg) and D-dimer (563.8–591.8 ng/mL), and preserving arterial architecture, but with significant BT prolongation. Clopidogrel reduced thrombus weight (4.18 mg), $TXB_2$, D-dimer (552.2 ng/mL), and MDA (4.19 µmol/L) without affecting CT and with intermediate effects on BT. Aspirin showed relatively modest effects across all outcomes. Anticoagulants also reduced histological damage and normalised leukocyte counts. The efficacy of the anticoagulants reflected their mechanistic targets in $FeCl_3$-induced carotid thrombosis, following the gradient of dabigatran ≈ apixaban > clopidogrel >> aspirin. In this platelet-dominant model, clopidogrel was surprisingly effective, whereas aspirin had effects. DOACs offered the inhibition of thrombus formation, albeit at the expense of increased bleeding liability.

## 1. Introduction

Thrombosis remains one of the principle causes of cardiovascular morbidity and mortality globally [1], requiring the invention of more effective pharmacological methods. One of the most

widespread methods used to induce carotid artery thrombosis in rat models is ferric chloride (FeCl3), which provides a precise method to study thrombus generation and assess potential antithrombotic drugs [2, 3]. This model offers robust endpoints such as occlusion time (OT), bleeding time (BT), capillary-tube clotting time (CT), and thrombus weights, which are essential for the measurement of both efficacy and safety [4, 5] While current antiplatelet therapies like aspirin and clopidogrel are very important, they can cause bleeding problems and do not work in the same way for everyone [6, 7]. Crucially, certain studies have suggested that the bleeding risk of apixaban and dabigatran may be comparable to that of aspirin—a notable finding for translational safety considerations [8].

The advancement of innovative antithrombotic medicines with enhanced efficacy and safety profiles continues to be a pivotal objective in cardiovascular research. Aspirin and clopidogrel remain the pillars of the antiplatelet strategy. Aspirin works through irreversible cyclooxygenase-1 in-activation, which blocks thromboxane $A_2$, and clopidogrel by $P2Y_{12}$ receptor inhibition in the platelet [9, 10].

Rising D-dimer levels signal that a clot is being broken down, while thromboxane $B_2$ ($TXB_2$) indicates that platelets are switching on. $FeCl_3$-induced tissue injury is closely associated with increased oxidative stress, which can be evaluated using malondialdehyde (MDA) as a biomarker of oxidative damage. This provides important insight into the extent of vascular and cellular injury caused by $FeCl_3$ exposure [5, 11]. Network meta-analyses indicate that apixaban is associated with a better safety profile, including less major bleeding, compared with rivaroxaban and dabigatran [12].

Despite being clinically successful, variability in patient response, resistance to these therapies, and increased bleeding risks are significant drawbacks. Consequently, there has been growing interest in exploring novel oral anticoagulants, including apixaban and dabigatran [13]. Direct thrombin inhibitor (DTI), or direct thrombin inhibitor (dabigatran), inhibits thrombin-induced platelet activation and the conversion of fibrinogen to fibrin by binding reversibly to both free and clot-bound thrombin, similar to apixaban, lowering the thrombus weight significantly [14]. It has a major impact on models of arterial damage. In arterial thrombosis models where platelet aggregation is the main cause, such as a model featuring $FeCl_3$-induced damage, clopidogrel is very efficient. It prolongs the OT regularly and significantly. Factor Xa inhibitor apixaban and DTI dabigatran have shown clinical improvement in both venous thromboembolism and atrial fibrillation, with less frequent need for therapeutic monitoring compared with vitamin K antagonists [15-17].

Although the $FeCl_3$-induced thrombosis model in rats is well established and the clinical benefits of antithrombotic drugs such as apixaban, dabigatran, clopidogrel, and aspirin are well documented, important gaps remain in the preclinical literature [14], one key limitation is the lack of direct comparative studies. Individual studies have generally evaluated only one of these agents separately [18], with limited studies comparing them directly in the same standard experimental framework. Because these drugs act via distinct pathways (Factor Xa blockade, direct thrombin blockade, $P2Y_{12}$ antagonism, and COX-1 blockade), therefore, head-to-head trials are necessary to produce unbiased comparisons in efficacy and safety between these agents prior to routine clinical use [14].

Moreover, most studies concentrate on one dominant endpoint, such as OT or thrombus weight, and without frequently investigating underlying mechanisms. For example, measures like thromboxane generation (for antiplatelet activity), oxidative stress from $FeCl_3$ injury, or D-dimer levels reflecting fibrinolysis are rarely evaluated in parallel within the same animals [19].

This study used a standardised $FeCl_3$-induced carotid artery thrombosis model in rats to systematically evaluate and compare the antithrombotic efficacy and safety profiles of apixaban, dabigatran, clopidogrel, and aspirin. To provide an integrated evaluation of therapeutic effectiveness and mechanistic outcomes, a wide range of parameters were evaluated, including vascular OT, BT, CT, serum $TXB_2$, D-dimer concentrations, thrombus weight, MDA levels, haematological and biochemical indices, and histopathological changes.

## 2. Related Works

Experimental animal models of arterial thrombosis have been well established to explore the pathogenesis and to evaluate antithrombotic intervention. The $FeCl_3$–induced carotid artery thrombosis model is one of the most commonly used because it is reproducible and can mimic oxidative

endothelial injury, which causes platelet-rich thrombus formation [3, 5, 20, 21]. The animal model results in endothelial denudation and subendothelial collagen exposure by redox stress, leading to platelet adhesion, aggregation, and fibrin deposition [22, 23]. Further standardisation has consensually adopted the time to occlusion and thrombus weight as test guidelines, which increase its reliability for assessment of drug impacts [8, 24].

Recently, substantial strides have been made in the form of direct oral anticoagulants targeting individual coagulation factors. Apixaban is a direct factor Xa inhibitor with predictable pharmacokinetics, a wide safety margin, and strong antithrombotic efficacy in human14 and rodent thrombosis models [14, 15, 25, 26]. Likewise, dabigatran, a direct thrombin (Factor IIa) inhibitor, effectively inhibits the establishment of fibrin and prevents further thrombus growth in the $FeCl_3$ and laser-injury models [19, 27- 29]. Two drugs decrease thrombus burden and plasma D-dimer levels, indicating coagulation activation is effectively inhibited [30-32]. Moreover, several studies have determined that the aforementioned new FXI inhibitors achieve similar efficacy with fewer bleeding episodes, suggesting a potential direction transforming anticoagulation therapy [1, 10, 17].

Antiplatelet drugs such as aspirin and clopidogrel remain fundamental drugs in the treatment of arterial thrombosis due to their specific mechanisms of action on platelet activation. Aspirin works by irreversibly inhibiting cyclooxygenase-1 (COX-1), which reduces the production of thromboxane $A_2$ and subsequently decreases platelet aggregation [33-35]. In contrast, clopidogrel inhibits ADP-induced platelet activation through selective antagonism of the $P2Y_{12}$ receptor. This inhibitory effect results from direct $P2Y_{12}$ receptor blockade and is independent of thromboxane $A_2$ formation or experimental calculations related to thromboxane release. Clopidogrel therefore suppresses platelet activation by preventing signalling mediated by adenosine diphosphate (ADP), effectively reducing platelet aggregation and thrombus formation [36]. While such drugs are effective for this purpose, they may not provide the extent of thrombus inhibition seen in $FeCl_3$-induced models as produced by anticoagulants because they largely target platelet rather than plasma coagulation pathways [6, 7, 37].

Recent data indicate that oxidative stress, inflammation, and vascular dysfunction are key components of the prothrombotic milieu in $FeCl_3$ injury [23, 38- 40]. Agents with antioxidant/endothelial-protective function, such as melatonin, have been found to protect endothelium and prevent thrombus formation when administered alone or in combination with anticoagulants [41-43]. These findings highlight the value of targeting both coagulation and oxidative pathways simultaneously.

Nevertheless, few studies have directly compared several different antithrombotic drugs using one procedural model. Most prior studies have focused on individual drug classes, restricting the ability to interrogate mechanisms and translations. Therefore, this study performs a comprehensive comparative evaluation of apixaban, dabigatran, clopidogrel, and aspirin in $FeCl_3$-induced carotid artery thrombosis in rats, focusing on haemostatic parameters, oxidative stress biomarkers, and histopathological outcomes.

## 3. Materials and Methods

### *3.1. Chemicals and Drugs*

The chemicals and pharmaceutical products used in this study included $FeCl_3$ hexahydrate, formula: $FeCl_3 \cdot 6H_2O$, molecular weight: 270.30 g/mol, purity (ACS grade): 97%, CAS NUMBER: 10025-77-1, India. The following commercial drugs were used in this study: Plavix (clopidogrel, 75 mg film-coated tablets; Sanofi, France), Trombolik Cardio (acetylsalicylic acid, 100 mg gastro-resistant tablets; Nobel İlaç, Turkey), Pixan (apixaban, 5 mg film-coated tablets; Alfa Pharma, Egypt), and Pradaxa (dabigatran etexilate, 110 mg hard capsules; Boehringer Ingelheim, Germany).

### *3.2. Animals and Housing*

Adult male albino rats (250–330 gm) were supplied from the Animal House, Biology Department, College of Science, University of Raparin. Breeding in the animal house was controlled, and rats were maintained under standard laboratory conditions (12-hours light/dark cycle, temperature 22 ± 2°C) with free access to food and water. Male rats were chosen to minimise hormonal variability as

fluctuations in oestrogen and progesterone during the female oestrous cycle can alter thrombosis outcomes [44, 45]. Rats were maintained on a non-standard diet prepared by the authors of wheat (66.6%), soya (25.6%), sunflower oil (4.3%), limestone (1.5%), AZ/1200 (0.08%), salt (0.64%), dicalcium phosphate (0.64%), methionine (0.158%), lysine (0.244%), choline chloride (0.062%), and trace elements (0.05%).

### 3.3. Ethical Approval

All animal procedures were performed in strict accordance with established ethical guidelines for animal research. The study protocol was reviewed and approved by the Animal Ethics Committee of the University of Raparin (Approval No: 2866/28-5-2023, approved on 14 September 2025). Experiments were conducted following the institution's policies for the care and use of laboratory animals, and every reasonable measure was taken to minimise the number of animals used and to safeguard their comfort, health, and welfare throughout the study. All work adhered to internationally accepted principles for humane animal handling.

### 3.4. $FeCl_3$-induced Thrombosis in Carotid Rats

A rat model of thrombosis was induced by $FeCl_3$. The rats were anesthetised via an intraperitoneal injection of ketamine (80 mg/kg) plus xylazine (10 mg/kg) 15–20 mins before surgery. Rats were placed on a heating pad to maintain body temperature after anaesthesia. Under a dissecting microscope, the left carotid artery was exposed and a small segment of filter paper (2 * 4 mm) soaked in a 35% $FeCl_3$ solution was applied directly to the surface of the artery for 10 min to induce the thrombus formation. After the exposure period, the filter paper was removed, and the artery was left in situ for an additional 60 minutes to allow for stable thrombus development [46].

### 3.5. Experimental Design

A total of 45 rats were randomly allocated into six experimental groups, with seven rats in each group except for the $FeCl_3$-only group, which included 10 rats. The groups were organised as follows:

- Control group: filter papers were saturated with normal saline instead of $FeCl_3$.
- $FeCl_3$ group: rats received oral administration of 1% ethanol prior to thrombosis induction.
- $FeCl_3$ + Apixaban group: rats were pre-treated with apixaban (5 mg/kg, orally), dissolved in 1% ethanol, two hours before induced thrombosis by $FeCl_3$.
- $FeCl_3$ + Dabigatran group: rats were given dabigatran (15 mg/kg, orally), dissolved in 1% ethanol, 30 minutes before thrombus induction.
- $FeCl_3$ + Clopidogrel group: rats were administered clopidogrel (30 mg/kg, orally), dissolved in 1% ethanol, two hours before $FeCl_3$ exposure.
- $FeCl_3$ + Aspirin group: rats were treated with aspirin (30 mg/kg, orally), dissolved in 1% ethanol, two hours before thrombus induction.

### 3.6. Justification of Drug Dosages

Aspirin, clopidogrel, apixaban, and dabigatran etexilate were given at antithrombotic and anticoagulant doses described in established validated rodent models. Aspirin (30 mg/kg, orally) is the most commonly used intervention for adequate suppression of platelet COX-1 activity and thromboxane $A_2$ production. Previous studies have demonstrated that aspirin given at a dose of 10–30 mg/kg to rats [47, 48]. Clopidogrel (30 mg/kg, orally) has been widely used in previous studies; 10–30 mg/kg of the compound are able to produce potent inhibition and robust antithrombotic effects on the P2Y12 receptor [46, 47]. The animals were orally administered a dose of 5 mg/kg apixaban, which is in the experimentally effective dose range of 5–10 mg/kg, resulting in an anticoagulant effect and achievement of therapeutic plasma levels in rats [48, 49]. Dabigatran was given orally at 15 mg/kg, which falls in the middle of therapeutically relevant doses (e.g., 5–30 mg/mL/kg under laboratory settings) reported to yield consistent thrombin inhibition and attenuate thrombogenesis in rodents [50, 51]. Thus, these two doses were chosen for this study as physiologically effective and literature-supported concentrations to evaluate their antithrombotic activity.

### 3.7. Determination of Occlusion Time, ClottingTime, and Bleeding Time

Thrombotic occlusion was monitored by recording distal artery temperature with a thermometer. OT was the time that elapsed from laying the $FeCl_3$-soaked filter paper on the artery to a rapid fall in temperature. The distal location was selected because this represents flow at a distance from an injury. The temperature should be constant when blood flow is normal, and a marked decrease in temperature indicates that blood flow has been reduced (or stopped), which is the first change in thrombosis. CT was assessed using the capillary tube method. Fresh blood was drawn and placed into heparin-free capillary tubes, and the time taken for a visible fibrin clot to form at room temperature was recorded. BT was assessed using the tail transection method, where absorbent paper was applied to the wound until no blood was absorbed onto the paper; this wicking was done every 15 seconds, and the time was recorded until bleeding stopped. These measurements were performed using established experimental methods as previously de-scribed in the literature [2, 3, 6].

### 3.8. Determination of Thrombus Weight

At the end of the experimental period, all the rats were humanely euthanised under deep anaesthesia using ketamine (80 mg/kg) and xylazine (10 mg/kg), followed by confirmation of death through loss of reflexes and respiratory arrest per internationally accepted ethical principles. The carotid artery was dissected with caution, and the part including the thrombus was resected and incised longitudinally. The thrombus was gradually detached from the arterial wall with fine forceps. The isolated thrombus was placed directly into a weighed microcentrifuge tube and then re-weighed on an analytical balance. The weight of the thrombus was determined by subtracting the weight of the empty tube from the combined weight, which gave a direct measure of the thrombus burden.

### 3.9. Determination of Thromboxane and D-dimer

Blood was obtained from the cardiac puncture into a gel tube for thromboxane and sodium citrate tube for D-dimer. The levels of serum $TXB_2$ and plasma D-dimer were measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits (Sunlong Biotech; Cat. SL0678Ra for $TXB_2$ and SL1303Ra for D-dimer) according to the manufacturer's instructions. In short, antibody pre-coated pates from standards and samples were incubated with horseradish-peroxidase-conjugated detection antibodies. The wells were washed thoroughly to remove unbound substances, and colour was developed with a TMB substrate, and the producer was halted with a stop solution. Absorbance was measured at 450 nm with a microplate reader, and concentrations were calculated from the corresponding standard curves. Thromboxane $B_2$ and D-dimer measurements were performed using established analytical meth-ods as previously described in the literature [9, 18].

### 3.10. Determination of Malondialdehyde

Serum was mixed with 17.5% trichloroacetic acid (TCA) for deproteinization and subsequently with 0.66% thiobarbituric acid (TBA). The solution was vortexed and placed in a water bath at 95 °C for 45 min and cooled to room temperature. The samples were centrifuged at 2000 rpm for 15 min after 70% TCA was added and mixed. The pink-coloured supernatant was transferred to a cuvette, and absorbance was read at 532 nm using a spectrophotometer. MDA concentration (μmol/L) was determined using the thiobarbituric acid reactive substances (TBARS) method [32].

### 3.11. Haematological analysis

Whole blood was collected from each rat by cardiac puncture into dipotassium ethylenediaminetetraacetic acid K2-EDTA tubes to prevent coagulation. Samples were gently inverted, kept on ice, and analysed within 2 h of collection. Total white blood cell count (WBC) and differential leukocyte counts (neutrophils, lymphocytes, monocytes, basophils, and eosinophils) were determined using an automated haematology analyser (Swelab 5-part Analyzer; Boule Diagnostics AB, Stockholm, Sweden) according to the manufacturer's instructions and laboratory quality-control procedures. These data were used to evaluate haematological changes associated with $FeCl_3$-induced thrombosis and to compare the effects of the study drugs. Haematological parameters were determined using standard analytical procedures [6].

### 3.12. Histological Cross-section of Carotid Artery

The carotid artery was removed from the anesthetised animals, and they were immediately fixed in formalin saline (10%), followed by dehydration using a series of graded ethanol in ascending concentrations (50%, 70%, 95%, and 100%). The animals were then immersed in xylene for clearing and infiltrated with paraffin wax, and the tissues were embedded in paraffin wax. Four-micrometre-thick paraffin sections were obtained by using a rotary microtome (Bright Instrument Co. Ltd., Cambridge, UK) and stained with haematoxylin and eosin (H&E). The specimens were examined and photographed under a light microscope (digital binocular compound microscope 40x-200x, built-in 3MP USB camera; China). Histological processing and cross-sectional analysis of the carotid artery were performed using established experimental procedures [3, 38].

### 3.13. StatisticalAnalysis

All data were expressed as means ± standard error, and statistical analysis was carried out using available statistical software (Statistical Package for Social Science SPSS, version 27 and GraphPad Prism, version 9). Before inferential analysis, data normality was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. As the data were normally distributed, parametric statistical analysis using the F-test and one-way analysis of variance (ANOVA) was applied. Statistical significance was determined using one-way ANOVA followed by post-hoc Tukey's test for multiple mean comparisons at significant level of 0.05.

## 4. Results

Figures 1A–C present the OT, BT, and CT measured in all experimental groups. Topical application of $FeCl_3$ to the carotid artery produced a rapid thrombotic response, whereas the sham control (filter paper saturated with normal saline) did not form thrombi. Treatment with antithrombotic agents significantly prolonged OT compared with the $FeCl_3$ group (Figure 1A). Apixaban, dabigatran, and clopidogrel each produced a highly significant delay in vessel occlusion ($p < 0.0001$ versus $FeCl_3$), while aspirin produced a smaller but still significant prolongation of OT ($p < 0.01$ versus $FeCl_3$). Of the drugs tested, dabigatran and clopidogrel showed the greatest efficacy in delaying occlusion. BT results are presented in Figure 1B. The control group showed a moderate BT, and $FeCl_3$ alone produced a slight reduction in BT. Anticoagulant and antiplatelet treatments markedly prolonged bleeding compared with $FeCl_3$. Both apixaban and dabigatran caused large increases in BT ($p < 0.0001$ versus $FeCl_3$). Clopidogrel also produced a significant prolongation of bleeding ($p < 0.0001$), whereas aspirin induced a smaller but significant increase ($p < 0.01$). Figure 1C displays the results of the CT test. CT was modestly reduced by $FeCl_3$ compared with the control ($p < 0.05$). Apixaban and dabigatran significantly prolonged CT relative to the $FeCl_3$ group ($p < 0.0001$), consistent with their anticoagulant mechanisms. In contrast, clopidogrel and aspirin did not produce significant changes in CT compared with $FeCl_3$.

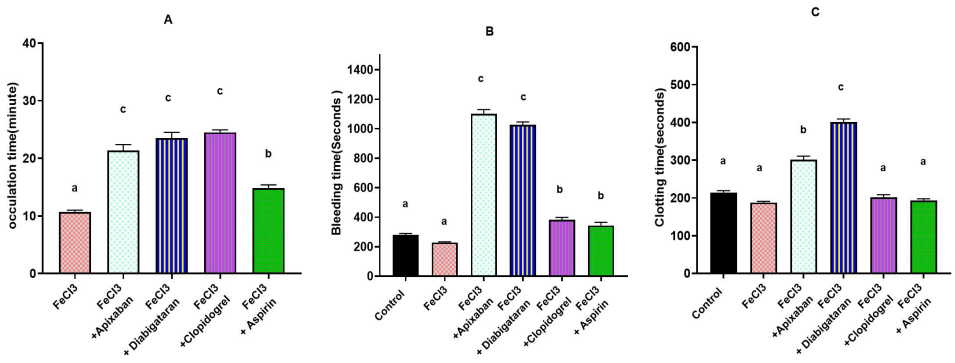


**Figure 1:** Effects of apixaban, dabigatran, clopidogrel, and aspirin on (A) occlusion time, (B) bleeding time, and (C) clotting time in ferric-chloride–induced thrombosis in rat carotid arteries, The control group was not included in occlusion time analysis because no arterial occlusion was observed in control animals. Different letters above the bars indicate statistically significant differences among groups according to one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test ($p < 0.05$).

Table 1 indicates that the application of $FeCl_3$ markedly promoted thrombus formation and increased serum biomarkers compared to the control; specifically, $FeCl_3$ caused significant increases in thrombus weight (mg), serum D-dimer, serum thromboxane, and MDA levels (all $p < 0.0001$ vs. control). Thus, antithrombotic drugs markedly suppressed these $FeCl_3$-induced alterations. Apixaban significantly decreased thrombus weight ($p < 0.0001$ vs. $FeCl_3$), D-dimer levels ($p < 0.001$), and MDA levels ($p < 0.0001$), but it had no significant effect on the serum thromboxane level. Dabigatran was associated with a marked decrease in thrombus weight ($p < 0.0001$ vs. $FeCl_3$), a significant decrease in D-dimer ($p < 0.01$), and a small but significant decrease in thromboxane ($p < 0.05$) and MDA ($p < 0.0001$). Thrombus weight was significantly decreased on clopidogrel compared with $FeCl_3$ ($p < 0.0001$), as well as D-dimer, thromboxane, and MDA (all $p < 0.0001$). In comparison, aspirin produced partial inhibition of thrombosis, which was significantly ($p < 0.01$ vs. $FeCl_3$) less efficient, producing significant decreases in D-dimer ($p < 0.05$), thromboxane ($p < 0.05$), and MDA ($p < 0.0001$).

**Table 1:** Effects of apixaban, dabigatran, clopidogrel, and aspirin on thrombus weight, serum D-dimer, serum thromboxane $B_2$, and serum MDA in ferric-chloride–induced thrombosis in rat carotid arteries.

| | *Thrombus Weight (mg)* | *Serum D-Dimer (ng/ml)* | *Serum Thromboxane $B_2$ (pg/ml)* | *Serum MDA (µmol/l)* |
|---|---|---|---|---|
| ***Control*** | | 200.100 ± 8.157[a] | 125.400 ± 5.169[a] | 2.990 ± 0.268 [a] |
| ***FeCl3*** | 7.178 ± 0.193[a] | 708.700 ± 28.010[c] | 549.700 ± 22.030[d] | 6.764 ± 0.215[d] |
| ***FeCl3+Apixaban*** | 3.967 ± 0.125[c] | 563.800 ± 17.610[b] | 507.200 ± 19.020[d] | 4.107 ± 0.226[b] |
| ***FeCl3+Dabigatran*** | 2.533 ± 0.245[d] | 591.800 ± 18.340[b] | 513.200 ± 14.790[d] | 4.283 ± 0.200[b] |
| ***FeCl3+Clopidogrel*** | 4.183 ± 0.130[c] | 552.200 ± 18.890[b] | 393.500± 13.570[b] | 4.193 ± 0.153[b] |
| ***FeCl3+Aspirin*** | 6.117 ± 0.162[b] | 634.700 ± 11.460[b] | 479.000 ± 22.820[cd] | 5.088 ± 0.079[c] |

Values are expressed as mean ± SD. Different superscript letters within the same column indicate statistically significant differences among groups according to one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test ($p < 0.05$). Groups sharing at least one common letter are not significantly different.

Table 2 shows the changes in total WBC and differential counts (neutrophils, lymphocytes, monocytes, basophils, and eosinophils) of all tested groups. WBC in the control group was significantly decreased after $FeCl_3$ ($p < 0.05$). From the treatment groups, dabigatran most markedly normalised WBC counts towards control levels ($p < 0.05$ vs $FeCl_3$). Clopidogrel and aspirin also increased WBC numbers vs. $FeCl_3$, but this was not statistically significant. Neutrophil counts were comparable between the control and $FeCl_3$ groups, with no significant alteration. Neutrophil values were elevated in all treatment groups, but no difference was statistically significant. Lymphocyte numbers in the control group trended down after $FeCl_3$ exposure. The responses to treatment varied, but none were statistically significant. Numbers of monocytes were slightly lower in the $FeCl_3$ group compared with controls. Monocytes rose in all treated groups; however, elevation did not reach statistical significance. Basophil percentage was reduced in the $FeCl_3$ group, and treatments induced small increases in basophils, although those differences were not significant. Eosinophilia decreased significantly following $FeCl_3$. Dabigatran and apixaban ($p < 0.05$ vs. $FeCl_3$) significantly enhanced eosinophil counts compared to those in the vehicle group; clopidogrel and aspirin had no effect.

**Table 2:** Effects of apixaban, dabigatran, clopidogrel, and aspirin on neutrophils, lymphocytes, monocytes, basophils, and eosinophils in ferric-chloride–induced thrombosis in rat carotid arteries.

| | **WBC count ($\times 10^9$/L)** | **Neutrophils ($\times 10^9$/L)** | **Lymphocytes ($\times 10^9$/L)** | **Monocytes ($\times 10^9$/L)** | **Basophils ($\times 10^9$/L)** | **Eosinophils ($\times 10^9$/L)** |
|---|---|---|---|---|---|---|
| **Control** | 8.944 ± 1.558[a] | 1.323 ± 0.273 [a] | 4.190 ± 0.991[a] | 0.208 ± 0.015 [a] | 0.022 ± 0.002 [a] | 0.268 ± 0.049[ab] |
| **FeCl3** | 4.343 ± 0.343[b] | 1.144 ± 0.176 [a] | 3.907 ± 0.467 [a] | 0.174 ± 0.045 [a] | 0.011 ± 0.002 [a] | 0.170 ± 0.020[a] |
| **FeCl3+ Apixaban** | 5.223 ± 0.728 [b] | 1.607 ± 0.235 [a] | 3.300 ± 0.631 [a] | 0.273 ± 0.052 [a] | 0.015 ± 0.003 [a] | 0.172 ± 0.024[b] |
| **FeCl3+ Dabigatran** | 8.560 ± 0.752 [a] | 1.755 ± 0.264 [a] | 5.075 ± 0.433 [a] | 0.321 ± 0.056 [a] | 0.030 ± 0.003 [a] | 0.2825± 0.024[b] |
| **FeCl3+ Clopidogrel** | 7.465 ± 1.135 [b] | 1.510 ± 0.180 [a] | 5.777 ± 1.019 [a] | 0.185 ± 0.040 [a] | 0.016 ± 0.003 [a] | 0.246 ± 0.037[a] |
| **FeCl3+ Aspirin** | 7.188 ± 1.231 [b] | 1.972 ± 0.294 [a] | 4.918 ± 0.912 [a] | 0.276 ± 0.101 [a] | 0.025 ± 0.002 [a] | 0.237 ± 0.040[a] |

Values are expressed as mean ± SD. Different superscript letters within the same column indicate statistically significant differences among groups according to one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test ($p < 0.05$). Groups sharing at least one common letter are not significantly different.

Histological examination of the carotid arteries revealed clear differences between the experimental groups. The control group rats (Figure 2A and Figure 3A) demonstrated a normal architecture of the arterial wall with an intact tunica intima in close contact with the lumen (blue arrow), a clear tunica media (red arrows), and a healthy tunica adventitia (yellow arrow). In contrast, the $FeCl_3$-induced thrombosis group without treatment (Figure 2B and Figure 3B) presented a broad thrombus (white line) with a lumen fully occluded by homogenously platelet-rich thrombi and red blood cells (black arrow), along with platelet adhesion on the endothelium (blue arrow). Apixaban-treated rats (Figure 2C and Figure 3C) have smaller thrombi, with a few red blood cells observed within the lumen (black arrows), which is kept more open (blue arrow). Administration of dabigatran (Figure 2D and Figure 3D) resulted in only a small amount of thrombus present (black arrows), with normal architecture maintained in both the tunica intima and media (blue and red arrows). In clopidogrel-treated rats (Figure 2E and Figure 3E), small thrombi could be observed (black arrows), with destroyed red blood cells lacking cellular structure and mild endothelial injuries with platelet adhesion (blue arrows). Animals treated with aspirin (Figure 2F and Figure 3F) also had both thrombi in the lumen (black arrows), homogenous red blood cells, and visible endothelial injuries with platelet adhesions (blue arrows). Collectively, these findings suggest that the treatment of antithrombotic agents led to dissimilar degrees of thrombus reduction and attenuation in arterial wall damage compared to the no-treatment thrombosis group for figures 2 and 3.

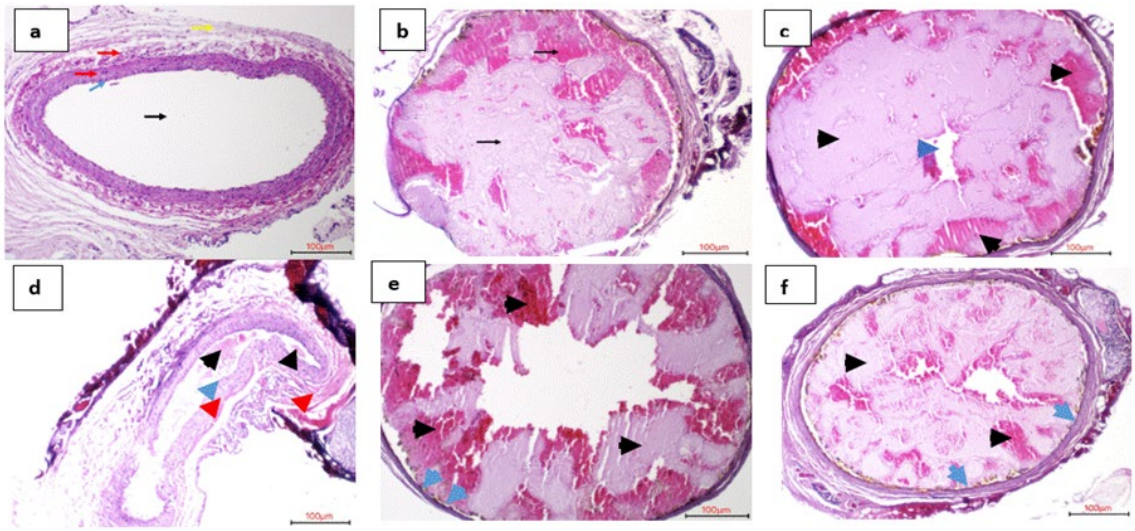


**Figure 2:** Histological cross-section of the carotid artery of (a) normal rats showing a normal structure. Histological cross-section of carotid artery thrombosis in rats (b) without using any drug, showing complete occlusion of the lumen; (c) treated with apixaban before induced thrombosis, showing a thrombus in the lumen; (d) treated with dabigatran orally administered to rats before thrombus induction, showing a small thrombus in the lumen; (e) treated with orally administered clopidogrel before the thrombus induction, showing a small thrombus in the lumen; (f) treated with aspirin orally administered before the thrombus induction, showing a thrombus in the lumen. Black arrows show lumen or thrombus location; black arrowheads indicate organized fibrin-rich thrombus; red arrows indicate platelet aggregation; blue arrows indicate endothelial lining; yellow arrows indicate inflammatory cell infiltration. (H&E stain, magnification ×200).

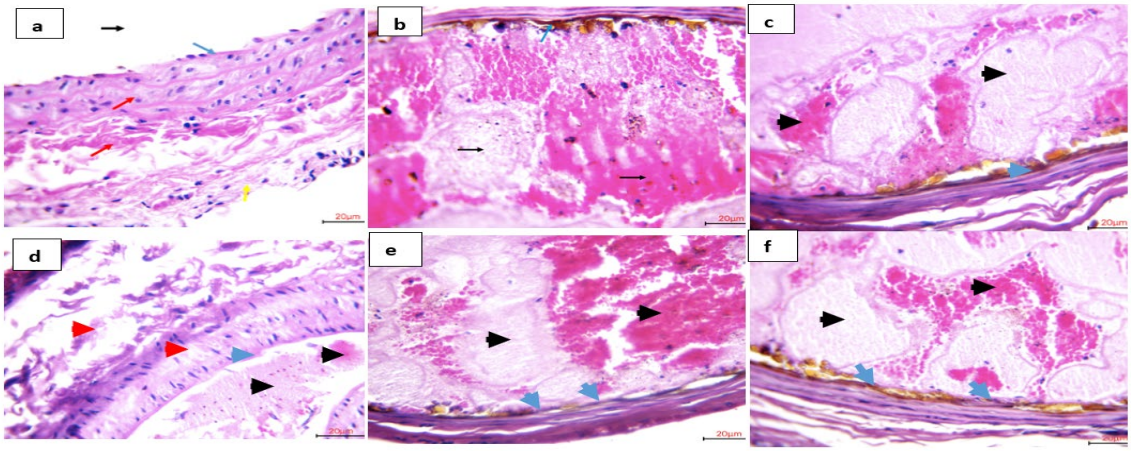


**Figure 3:** Histological analysis of the carotid artery is presented in a–f. The control group (a) presented normal vascular architecture, with well-defined tunica intima, media, and adventitia. In $FeCl_3$-rats (b), the thrombus was clearly formed, including platelet-rich and red blood cell accumulation with massive adhesion of platelets to the endothelium. (c) The number of cellular structures within the thrombus was lower after apixaban treatment; some organisation and platelet adhesion were still visible. (d) Dabigatran-treated rats manifested intact vascular structure with unaltered tunica intima and media. Both clopidogrel (e) and aspirin (f) groups demonstrated homogenous RBC appearance for thrombus formation, with endothelial material appearing to closely adhere to platelets. Black arrows indicate thrombus regions, red arrows indicate platelet aggregation, and blue arrows indicate endothelial lining or vascular wall structures. (H&E stain, magnification ×200).

## 5. Discussion

The experimental results, carefully collected in a $FeCl_3$-induced carotid artery injury model, provide deep comparative characterisations of the haemostatic profiles of four leading antithrombotic drugs. This model is considered one of the most representative and replicable models simulating human arterial thrombosis because it works to cause severe oxidative damage in the vascular endothelium, as seen in the rapid exposure of subendothelial collagen and the deposition of tissue factor [52]. This series of events results in the development of a cohesive platelet-rich clot with secondary stabilisation by cross-linked fibrin mesh. The strong specificity of this model is demonstrated by the control group, in which application of normal saline instead of $FeCl_3$ did not induce any thrombotic occlusion; this clearly demonstrates that the thrombosis observed in the experimental groups is an immediate pathological response to the chemical injury rather than an artefact of surgical preparation [20]. Consequently, the determination of OT, which is the primary measure of antithrombotic activity, demonstrated that all four investigational drugs were highly statistically significantly elevated in OT when compared to the $FeCl_3$ control. This pooled efficacy provides evidence of their common ability to interfere with thrombogenesis. Nevertheless, the profound difference in degree of efficacy is paramount, and this appears to be mechanistically related to their different molecular targets. The highly significant ($p < 0.0001$) prolongation of OT by dabigatran is principally due to its direct inhibition of thrombin. Thrombin serves as regulator of coagulation, promoting fibrin formation as well as potent platelet activation with inhibition of thrombin, thus providing a strong dual antithrombotic attack [8, 53, 27]. Similarly, the large impact of apixaban, with a p-value $< 0.0001$, derives from its upstream blockade of Factor Xa, which substantially blocks the thrombin burst necessary to generate significant amounts of fibrin [8, 54].

In sharp contrast, the most striking finding in this study may be the excellent efficacy of clopidogrel, which delayed occlusion at all doses to a similar degree as potent anticoagulants ($p < 0.0001$). This emphasises the platelet-dominant aspect of the $FeCl_3$ model. Through permanent inhibition of the P2Y12 ADP-receptor—a major amplification signal for platelet aggregation—clopidogrel deeply alters the fundamental structure of the evolving arterial thrombus [36]. On the other hand, aspirin was significantly ($P < 0.01$) less effective. This is consistent with the fact that aspirin acts only by blocking the thromboxane A2 path, while other powerful pathways, such as those stimulated directly by collagen and thrombin, remain intact, allowing a thrombus to form more readily [33].

This distinct hierarchy of antithrombotic potency is inextricably associated, however, with the essential trade-off of bleeding risk evaluated as endpoint BT. The examination of this safety parameter shows an unusual profile [8, 55]. The direct oral anticoagulants (DOACs) dabigatran and apixaban produced a potent and statistically significant ($p < 0.0001$) prolongation of BT. This strong impact is a direct result of the systemic inhibition of the coagulation cascade that is necessary to maintain the initial platelet plug after its stabilisation as an enduring clot [56]. Similarly, clopidogrel also significantly prolonged BT ($p < 0.0001$) by inhibiting the platelet aggregation essential for primary haemostasis. At the same time, as compared to other drugs tested in this study, the effect of aspirin on bleeding was less pronounced but still objective ($p < 0.01$), which correlated with its lower antiplatelet activity. Aspirin mildly impairs platelet plug formation, but to a much lesser extent than clopidogrel [57].

Furthermore, knowledge of CT data as determined by the capillary tube method is crucial and mechanistically conclusive. This is a measure of how long it takes to form a visible clot in fresh blood (a test using plasma with platelet inhibitors removed). The mark extension caused by dabigatran and apixaban (which is highly significant, $p < 0.0001$) is the only direct pharmacodynamic evidence of their anti-coagulant effect in blood circulation [34, 58]. This is because they both directly target enzymes in the coagulation cascade: dabigatran targets thrombin (the terminal enzyme generated during fibrin formation), whereas apixaban inhibits Factor Xa, which is vital for prothrombinase complex and consequently necessary for thrombin production. By obstructing these central events, they thus directly delay the overall process of fibrin polymerisation, and this is directly measured by the capillary tube method [28, 25].

On the other hand, it is a natural and expected consequence that neither clopidogrel nor aspirin had any significant effect on CT. The reason for this is that the capillary tube method, like other plasma-based coagulation tests, primarily assesses soluble coagulation factors. Antiplatelet drugs such as clopidogrel and aspirin modify the activity of cell components and platelets only by inhibiting activation and aggregation pathways [54, 33, 56]. They do not directly impair enzymatic reactions of the coagulation cascade that take place in vitro in plasma. Accordingly, in the test tube, where platelets are almost inactive, the plasma from animals treated with these drugs retains its full capacity to generate fibrin through the intrinsic pathway, resulting in a normal CT. This fact unambiguously demonstrates that their anti-thrombotic action is limited to platelet function and does not affect the kinetics of formation of a fibrin clot in plasma [36, 33].

To explain this, with $FeCl_3$, thrombus weight increases rapidly because, first, ferric ions catalyse local oxidative chemistry (Fenton reaction), which denudes the endothelium and exposes subendothelial collagen and the von Willebrand factor, thus immediately recruiting activated platelets [20, 22, 23]. Second, $FeCl_3$ induces red blood cell membrane damage, leading to haemolysis to release free haemoglobin/iron, which amplifies local coagulation and furnishes a scaffold for growth of the clot [18, 20]. Finally, tissue factor exposure along with activation of coagulation proteases [factor VIIa-thromboplastin pathway undergoing downstream amplification] to facilitate massive fibrin deposition in consolidating the thrombus [38]. As a consequence, anticoagulants (dabigatran and apixaban included) blunt thrombus weight for multiple mechanisms: they inhibit thrombin generation/ activity so that less fibrin matrix is generated, limit platelet activation prompted by local intense-thrombin episodes (reducing platelet participation to clot mass), reduce pro-inflammatory signalling promoted by thrombin in the venous wall (and consequently reduce the leukocyte traffic needed to fortress/resist stabilised thrombi) [41]. In addition, antiplatelet agents (clopidogrel, aspirin) reduce thrombus weight because they inhibit platelet aggregation and secretion (and thus the cellular core of the thrombus), decrease formation of platelet–leukocyte aggregates (promoting an inflammatory consolidation), and reduce release of platelet microparticles that facilitate coagulation. However, aspirin's smaller effect could be due to dominance of coagulation (fibrin) over platelets or suboptimal dosing/timing in a given analysis [59].

Consequently, D-dimer is a degradation product of cross-linked fibrin, and levels are therefore low under physiological conditions in control animals because minimal amounts of fibrin formation and subsequent fibrinolysis take place. Accordingly, $FeCl_3$-induced thrombosis is associated with

massive induction of D-dimer ($p < 0.0001$), indicating extensive fibrin generation and subsequent activity of the fibrinolytic system generating measurable fragments of D-dimer. In addition, vascular injury, haemolysis, and activation of inflammatory protease all speed up the process of clot formation and lysis, which also causes a higher level of circulating D-dimer [30, 60].

Thus, as dabigatran markedly suppresses thrombus formation and thrombin activity, it also attenuates fibrin generation, thus decreasing the amount of substrate available for fibrinolysis. D-dimer then decreases accordingly (dabigatran D-dimer $p < 0.01$ vs $FeCl_3$) [61]. Similarly, apixaban inhibits factor Xa activity, resulting in reduced generation of downstream thrombin and fibrin deposition. Hence, it was anticipated that D-dimer would decrease. Therefore, reductions of D-dimer after anticoagulation are mechanistically in concordance with attenuated clotting rather than producing a direct influence on fibrinolysis [30].

In contrast, clopidogrel reduced D-dimer ($p < 0.001$ vs $FeCl_3$), which likely reflects a secondary reduction in clot size and stability due to less platelet aggregation and therefore less overall fibrin deposition and subsequent fibrinolysis [62]. In contrast, aspirin did not significantly change D-dimer; this may be because aspirin's partial antiplatelet effect reduces platelet-driven aggregation but may be insufficient to substantially lower thrombin generation and fibrin formation in a model where $FeCl_3$ drives strong coagulation. As a consequence, D-dimer remains near $FeCl_3$ levels. This suggests that its mode of action is predominantly via platelet inhibition, with less effect on fibrin formation and clot stabilisation. Additionally, the above pattern is consistent with the interpretation that D-dimer follows fibrin burden, and anticoagulant actions directly reduce this more than interference with partial platelet activity in this model [31, 32].

Turning next to platelet activity, thromboxane was elevated after thrombosis was induced by $FeCl_3$ [63] because (1) endothelial denudation exposes collagen and other agonists, triggering platelet activation and COX-1–dependent biosynthesis of $TXA_2$; (2) thrombin generation in coagulation cascade further activates platelets and stimulates $TxA_2$ release; and (3) recruited leukocytes together with activated platelets form a reciprocal process that enhances the production of thromboxane. Accordingly, P2Y12 inhibition with clopidogrel markedly reduces thromboxane through inhibition of ADP-mediated platelet aggregation and release [62] because (a) when fewer platelets are activated, less $TxA_2$ is synthesised and (b) the contribution of platelets to further amplification of their own activation is attenuated. In contrast, anticoagulants (apixaban) do not directly inhibit platelet COX-1 and thus may fail to substantially alter thromboxane unless these agents markedly ablate thrombin-dependent platelet activation. Dabigatran may elicit a modest secondary reduction in thromboxane because blocking thrombin diminishes one major platelet agonist, and aspirin directly inhibits COX-1, with consequent reductions in TxA2, although the magnitude of the effect is impacted by timing, dose, and non-platelet sources of metabolites of TxA2 (e.g., leukocytes), which can dampen the measured change [62].

Moreover, as MDA is an end product of lipid peroxidation, the baseline (control) value of MDA in tightly sealed plates was low or normal. $FeCl_3$ generates local iron-catalysed oxidative chemistry (Fenton reaction), leading to haemolysis and leukocyte recruitment. As such, the levels of MDA should rise precipitately after $FeCl_3$ exposure ($p < 0.0001$), suggesting increased membrane lipid peroxidation in both the vasculature and the circulating compartment. What is more, the microenvironment of thrombus increases platelet activation and neutrophil oxidative burst, promoting MDA generation [64, 65]. Consequently, the varying influence of the antithrombotic agents on MDA levels indicates an interesting difference in their action beyond their common targets. The observation that a direct inhibitor of Factor Xa such as apixaban resulted in a strong decrease in MDA ($p < 0.0001$) is especially interesting. This would indicate that through the potent inhibition of coagulation pathways, apixaban may indirectly diminish an oxidative burst effect. Generation of thrombin is also known to activate inflammatory cells and stimulate reactive oxygen species (ROS) generation. Thus, by inhibiting the amplification of coagulation through Factor Xa, apixaban may attenuate the thrombin-mediated pro-oxidant signals, resulting in a significant reduction in lipid peroxidation [42].

Moreover, dabigatran exhibited a substantial reduction in MDA ($p < 0.0001$). Effect of dabigatran on the crosstalk between coagulation and oxidative stress. By inhibiting the activity of thrombin, a

central orchestrator of coagulation and inflammation, dabigatran may interrupt the cross-signalling process that potentiates ROS generation at the vascular injury site. Yet the small degree of more universal effect of dabigatran (which also significantly decreased thromboxane ≈ $p < 0.05$) indicates that it blocks the action of thrombin—itself a very strong platelet activator—which might result in somewhat broader suppression of both the micro-thrombotic and oxidative response compared with apixaban [66]. In contrast, the significant reduction in MDA levels observed with clopidogrel ($p < 0.0001$) may be attributed to its direct antiplatelet mechanism of action [52]. Activated platelets are an important ROS and pro-inflammatory mediator generator. By irreversibly inhibiting the P2Y12 receptor, clopidogrel is a powerful inhibitor of platelet activation and aggregation. Thus, it seems that the subsequent decrease in MDA is an indirect antioxidant effect, which may be due to its ability to reduce platelet-related oxidative stress. This places clopidogrel as an agent that specifically inhibits the platelet component of the oxidative response to thrombosis [42].

One of the most interesting findings is that aspirin induces only a partial but highly significant decrease in MDA ($p < 0.0001$), whereas its effect on thrombus weight reduction was not so strong. This potent antioxidant property would seem to be at least partially independent of the relatively weak antiplatelet effect in the model. One mechanism may be salicylate, the major metabolite of aspirin, which has direct free radical scavenging effects. In addition, aspirin can block NF-κB, a master transcription factor in the expression of pro-inflammatory and prooxidant genes. Regarding a potent decrease in MDA by aspirin, it suggests an interesting one among additional antioxidant properties that could provide vasculature with protection even beyond its COX-1 inhibiting effect [39].

Furthermore, the data from Table 3 are important for understanding systemic inflammatory and immunological responses during $FeCl_3$-induced arterial thrombosis [38]. Interestingly, there was a significant decrease in total WBC counts in the $FeCl_3$ group, as compared with the control ($p < 0.05$) [40]. This leukopenic response could be interpreted as marking specific physiological stress or as a process called ‘margination’, where activated leukocytes adhere to injured endothelium at the site of injury and to the developing thrombus itself, thus transiently depleting circulating cell numbers [67, 68]. This phenomenon is part of the growing concept of ‘immunothrombosis’, where innate immune cells are active participants in thrombus development. Thus, the WBC decrease argues that the $FeCl_3$-induced thrombotic event is neither a strictly localised phenomenon nor causes an unrecordable systemic inflammatory response [67].

In particular, between the treated groups, dabigatran had the greatest effect on normalising total WBC count and significantly increased compared to the $FeCl_3$-group ($p < 0.05$). This effect can be mechanistically linked to dabigatran's primary action as a DTI, besides being a powerful pro-inflammatory substance, as described in relation to its coagulation activities, is also able to activate endothelial cells and increase the expression of adhesion molecules that promote leukocyte adherence [69, 43]. This suggests that through thrombin inhibition, dabigatran is able to decrease leukocyte adhesion and sequestration into the vessel wall, leading to its higher numbers in circulation. This indicates that the anti-coagulant effect of dabigatran may provide an indirect anti-inflammatory property by inhibiting the spread of thrombin-induced coagulation and inflammation [68].

Notably, the most striking and statistically significant finding in the differential counts pertained to eosinophils, which were significantly decreased after $FeCl_3$ injury. Eosinophils are granulocytes traditionally related to allergic reactions and immune processes against parasites; however, evidence suggests that they exert a modulating effect on inflammation and thrombosis. Their absence in this model might indicate a stress-induced response or a specific recruitment to the thrombotic focus [70, 71]. The observation that both dabigatran and apixaban raised the reduced eosinophil numbers to significantly different degrees ($p < 0.05$) indicate a dedicated crosstalk between the coagulation cascade and eosinophil biology. Because they block two important steps of coagulation (thrombin and Factor Xa), this action indicates that coagulation proteases (either by a direct or indirect mechanism) may inhibit eosinophil production or viability, which is counteracted by their blockade [72].

Conversely, clopidogrel and aspirin were not found to have statistically significant associations with eosinophil counts. This differential effect clearly distinguishes the action of anticoagulants from that of antiplatelet agents. Although they act upon the platelets, they do not directly inhibit the

coagulation proteases that may be involved in eosinophil regulation [37]. The lack of significant trends in other differential counts (neutrophils, lymphocytes, monocytes) across treatment groups, particularly with clopidogrel and aspirin, also indicates that antiplatelet therapy has a more modest influence on the global leucocyte profile in this acute model compared to direct anticoagulation [73, 74].

The different biological effects of the treatments are graphically demonstrated by the histological examination. Indeed, the fact that dabigatran treatment left 'only a small amount of thrombus' and an intact appearance of the tunica intima and media is a compelling demonstration of its mode of action. Dabigatran is a DTI that inhibits the final common pathway of coagulation [21, 24]. As a result, it is a potent inhibitor of both fibrin generation and thrombin-induced platelet activation, resulting in a significant decrease in the size and stability of the thrombus. The conservation of the vessel wall architecture also indicates that dabigatran acts to attenuate secondary damage to the vessel wall via thrombin blockade, which is a potent mediator of inflammation and endothelial disturbance [29]. The marked reduction of the thrombus as well as a more patent lumen observed with apixaban was reminiscent of its action as a direct inhibitor of Factor Xa. By inhibiting factor Xa, apixaban prevents the development of thrombin and the subsequent effects on the blood coagulation system because thrombin-mediated effects, including platelet activation and ultimately fibrin clot formation. Only a very small number of red blood cells are found in the lumen, suggesting that the thrombus is likely friable and unstable, which can be seen in effective anticoagulation [26, 75].

In contrast, the histological patterns for the antiplatelet drugs clopidogrel and aspirin differed. Thrombi were present after both regimens, but they were of a different nature. The 'destroyed red blood cells' and 'platelet adhesion' findings in the clopidogrel group and the 'homogenous red blood cell' with platelet adhesions in the aspirin group are very interesting. These results accord with the main action of these drugs, namely, inhibition of platelet aggregation. Thus, they are less potent in inhibiting the deposition of fibrin and red blood cells in the lumen than they are in preventing a large, consolidated platelet-rich plug because the coagulation cascade is still largely intact. The 'gentle injuries' of the endothelium seen indicate that antiplatelet drugs do not act by a direct protection of endothelium against $FeCl_3$-induced oxidative damage but rather block platelets' response to such damage [35, 76, 77].

The current study possesses a number of important strengths, such as application of the $FeCl_3$-induced carotid artery thrombosis model; comprehensive evaluation of antithrombotic efficacy by multiple endpoint measurements including OT, thrombus weight, biochemical markers (D-dimer and TBX-$B_2$); and detailed histopathological examination. This integrated strategy improves the robustness of the cross-sectional analysis and provides insight into mechanisms that mediate differential effects between anticoagulant and antiplatelet agents. However, there are potential limitations. First, the present study was performed on a single animal species, which may restrict the direct transposition of the findings to human clinical applications. Second, the relatively short observation period did not allow assessment of long-term thrombus stability or vascular remodelling. Further experiments with multiple animal species, prolonged follow-up, and advanced haemodynamic monitoring would enhance the translational potential.

## 6. Conclusions

In the $FeCl_3$-induced thrombosis model in rats, all drugs tested exhibited antithrombotic properties; among the tested drugs, dabigatran and apixaban (DOACs) expressed the most evident effects by significantly slowing time to occlusion as well as reducing thrombus weight, though with a higher bleeding risk. Clopidogrel was as effective as anticoagulants, confirming the paramount role of platelets in this model, while aspirin was less effective. The findings highlight distinct molecular mechanisms, with anticoagulants providing broader anti-inflammatory and endothelial protection, whereas antiplatelet agents primarily target platelet activation. Overall, the present study highlights the inevitable trade-off between efficacy and bleeding risk, epitomises the molecular complexity of antithrombotic treatment with a gradient of potency—dabigatran ≈ apixaban > clopidogrel >> aspirin—and serves as confirmation regarding the relative efficacy and safety inherent to anticoagulation therapy. These results not only support the $FeCl_3$ model as a reliable instrument for studying translational

thrombosis but also provide mechanistic insight that could guide rational therapeutic selection and combination strategies for arterial thrombotic disorders.

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