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Review Article

Optimizing Hemostatic and Antithrombic Therapies: A Comprehensive Stewardship Strategies

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ABSTRACT

Optimizing hemostatic and antithrombotic therapies in clinical practice requires a robust and systematic approach to ensure patient safety, therapeutic efficacy and adherence to evidence-based guidelines. The tertiary care setting's appropriate use of hemostatic and antithrombotic drugs is optimized through the deployment of a comprehensive stewardship strategy, as described in this abstract. The stewardship program's main goal is to reduce bleeding and thrombotic events. To achieve this, the most recent American College of Cardiology/ American Heart Association (ACC/AHA) recommendations for therapeutic optimization are being implemented. Standardized protocol development, ongoing education for healthcare personnel and real-time decision support systems are important elements of the approach. The stewardship team, comprising multidisciplinary experts, conducts regular audits and feedback sessions to monitor adherence to prescribed guidelines and identify areas for improvement. Patient outcomes are assessed through various metrics, including medication adherence, satisfaction, quality of life and cost-effectiveness, using meticulously designed self-administered questionnaires. Preliminary data suggest a significant reduction in adverse events and improved patient outcomes, highlighting the potential of stewardship programs in optimizing anticoagulant and antithrombotic therapy. In order to improve patient safety and results, a more widespread deployment of this descriptive analysis throughout healthcare systems is advocated. It emphasizes the significance of a coordinated, evidence-based approach to the handling of drugs. This review concludes by addressing the complexities of hemostatic and antithrombotic therapies, this stewardship model demonstrates the critical role of interdisciplinary collaboration and continuous quality improvement in modern healthcare.

Keywords: Anticoagulants, Antithrombotic, Education, Multidisciplinary, Stewardship.

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INTRODUCTION

Anticoagulants, which are frequently used to treat and prevent Venous Thromboembolism (VTE) and to prevent stroke in patients with atrial fibrillation, are significant risk drugs, especially for those 65 years of age and older. They frequently result in adverse drug events and emergency room visits. Direct Oral Anticoagulants (DOACs) have become more popular than Vitamin K Antagonists (VKAs) due to their predictable pharmacokinetics, fixed dosing and fewer interactions, though they still require careful management. The Anticoagulation Forum's 2016 guidelines recommend specialized DOAC anticoagulation services to optimize care during transitions, which can reduce readmissions and adverse events.[1]

For Anticoagulation Stewardship Programs (ASPs), the US Anticoagulation Forum released guidelines in 2019 with the goal of improving the safety and effectiveness of anticoagulant use in a variety of care settings.[2] Following these recommendations, a tertiary care hospital created a multidisciplinary Anticoagulation Stewardship Program (ASP) with the goals of optimizing inpatient anticoagulant prescriptions, improving patient outcomes and cutting costs.[1] Hemostatic and Antithrombotic (HAT) medications, which are high-risk and costly, require diligent monitoring and dosage adjustments to prevent complications. The hospital's HAT Stewardship program involves a team of pharmacists, cardiologists and medical directors who oversee the appropriate use of these agents, develop treatment protocols and manage care transitions to improve patient outcomes and reduce adverse effects.[3] The optimization of hemostatic and anti-thrombotic therapies improves patient outcomes by balancing the bleeding risk and thrombotic events. It enhances the clot prevention, reduces complications and adverse effects and personalizes treatment strategies. These leads to better outcomes, reduced mortality and improved quality of life.

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HEMOSTATIC SYSTEM

One common medical intervention for thromboembolic consequences in vascular disease, both primary and secondary, is anticoagulation. In a variety of therapeutic situations, such as atrial fibrillation, Venous Thromboembolism (VTE), acute coronary syndromes and following cardiac surgery, Vitamin K Antagonists (VKAs) are beneficial in preventing and treating thrombotic disorders. Regular laboratory monitoring is required to maintain VKAs within a therapeutic range and minimize side effects, with bleeding being the most serious concern.[4] Serious bleeding is defined as either life-threatening or as harming essential organs and requiring intensive medical care, according to the International Society of Thrombosis and Haemostasis (ISTH). Prothrombotic processes, increased heart effort and hemoglobin reduction are some of the negative effects of short-term bleeding. The degree and duration of anticoagulation are important determinants in bleeding risk and the CHADS2 level is a valid indication of the risk of bleeding and stroke.[5]

Due in part to decreased metabolic clearance in older individuals, especially women, increasing age is linked to an increased risk of bleeding following VKA treatment. Bleeding risk and VKA needs can also be affected by genetic variables, such as polymorphisms in the VKORC1 and cytochrome P450 2C9 gene. Bleeding risk is greatly increased by comorbidities such as diabetes, liver or renal illness and congestive heart failure. Prospective bleeding issues are especially likely to occur in those with a history of gastrointestinal bleeding. Blood pressure control is crucial in preventing bleeding during VKA therapy.[6]

In older adults, co-medication significantly raises bleeding risk. Bleeding problems are significantly more likely in patients on VKAs when non-selective NSAIDs, COX-2 inhibitors, aspirin, or other antiplatelet medications are used. Severe thrombotic issues, such as venous thrombosis and thromboembolism, are often linked to deficiencies in anticoagulant components like antithrombin, protein C and protein S, which can increase thrombotic risk by 20-fold.[7] The coagulation process was shown in Figure 1.

ANTI-THROMBOTIC DRUGS REVIEW

Haemostatic drugs play a crucial role in maintaining haemostasis and reducing mortality associated with haemorrhage. Blood transfusions, which are performed in approximately 21% of all procedures and 45.8% of cardiac surgeries, are linked to several risks and adverse effects, including immunomodulation, bacterial infection and other serious non-infectious complications. Cardiovascular surgeons face the challenge of selecting from an expanding array of haemostatic agents, each with unique properties and varying levels of evidence supporting their use. While these agents are effective in reducing bleeding during surgeries, none fully embody the ideal characteristics of a haemostatic agent, though some can achieve haemostasis in under 10 min. Given the increasing variety of haemostatic drugs, understanding their mechanisms and differences is essential for choosing the most effective option to improve patient outcomes.[8]

When anticoagulants are combined with Dual Antiplatelet Treatment (DAPT), there is a higher chance of bleeding. Approximately 1.8 times increased bleeding risk is associated with DAPT compared to single antiplatelet medication (e.g., aspirin alone). As a side effect of antithrombotic medications, bleeding is most prevalent. There is a minimum 2.5-fold increase in risk when using aspirin in addition to a therapeutic dosage of a vitamin K antagonist (VKA), such as warfarin. An increase in ischemia events and mortality of five times and four times, respectively, can occur when antithrombotic medication is stopped due to significant bleeding. Studies have corroborated these worries by demonstrating that low-dose Direct Oral Anticoagulants (DOACs) reduce bleeding and work just as well as standard doses in three different situations: patients with stabilized Acute Coronary Syndrome (ACS), patients undergoing PCI for Atrial Fibrillation (AF) and patients receiving prolonged treatment for Ventilator-Associated Hemorrhage (VTE). VKAs have traditionally served as the cornerstone for the administration of full-dose anticoagulants; nevertheless, dosage adjustments are required for optimum effectiveness in order to maintain an International Normalized Ratio (INR) greater than 2.[9] A comprehensive overview of anti-thrombotic agents are shown in Table 1.

STRATEGIES OF HEMOSTATIC AND ANTI-THROMBOTIC AGENTS

Patients suffering from Atrial Fibrillation (AF) frequently have concurrent Acute Coronary Syndrome (ACS) and Coronary Artery Disease (CAD). Anticoagulants are frequently more advantageous than either single antiplatelet therapy or Dual Antiplatelet Therapy (DAPT) for the prevention of stroke in individuals with Atrial Fibrillation (AF). If stent thrombosis is your concern, DAPT is a better alternative than Vitamin K Antagonists (VKAs). DAPT plus a VKA combined in triple therapy has become standard treatment for AF patients undergoing Percutaneous Coronary Intervention (PCI). Even with these successful methods, there remains a 12% yearly chance of major bleeding.[10]

Antithrombotic medications used in PCI patients with AF have shown encouraging improvements in safety recently. The findings of the WOEST trial showed that bleeding rates were considerably lower with triple treatment a combination of aspirin, clopidogrel and a variable-knowledge additive than with dual therapy, which included clopidogrel and a VKA, at 6.5% vs 12.7% (HR, 0.49; 95% CI, 0.28-0.86). As such, guidelines now suggest dual therapy rather than triple therapy for these individuals. Data also indicate that, in comparison to triple therapy with a VKA and DAPT,

dual therapy with clopidogrel and a Direct Oral Anticoagulant (DOAC) lowers bleeding risk by over 50%.[11]

The PIONEER-AF research included 2,124 AF patients having PCI and examined two reduced-dose rivaroxaban regimens. The first combination involved taking 15 mg of rivaroxaban daily along with clopidogrel; the second involved taking 2.5 mg of rivaroxaban twice a day together with a low-dose of aspirin and clopidogrel. The patients were given a triple therapy regimen that included warfarin, clopidogrel and aspirin. Similar MACE rates across regimens demonstrated comparable efficacy. Aspirin, a P2Y12 inhibitor and warfarin were the three medications given to 2,725 AF patients included in the REDUAL-PCI study. A P2Y12 inhibitor was used in combination with dabigatran (110 mg or 150 mg twice day) as part of a dual treatment. With hazard ratios of 0.52 (95% CI, 0.42-0.63) and 0.72 (95% CI, 0.58-0.88), respectively, there were no discernible increases in Major Adverse Cardiovascular Events (MACE) or unscheduled revascularization when comparing the 110 mg and 150 mg doses of dual therapy to VKA-based triple therapy, which showed fewer clinically significant bleedings.[12]

Table 1: Review of Hemostatic agents.

Characteristics	Explanation
Role of Hemostatic Agents	It plays a vital role in preserving hemostasis and lowering hemorrhage-related mortality.
Blood Transfusion	Approximately 21% of all procedures and 45.8% of heart surgeries is associated with risk such as immunomodulation, bacterial infection and non-infectious infections.
Challenges for physician	To select a various hemostatic drug with distinct qualities and varying degrees of documentation.
DAPT vs Single Antiplatelet agents	DAPT increases the bleeding risk 1.8 times than single antiplatelet agents.
Aspirin+VKA	At therapeutic dose, these medications increase the bleeding risk of 2.5 times.
DOAC vs VKA	IN ACS, PCI for Atrial fibrillation and long-term Venous thromboembolism treatment, low-dose DOAC's are effective as conventional doses in reducing bleeding.
VKA	Traditional methods for full-dose anticoagulant management, requiring dosage adjustments to maintain INR>2 for optimal effectiveness.

Through their mechanisms of action, antiplatelet drugs and Direct Oral Anticoagulants (DOACs) specifically target the thrombotic process. Apixaban, edoxaban and rivaroxaban are examples of direct oral anticoagulants that block factor Xa, whereas dabigatran inhibits thrombin, lowering the production of fibrin. Whereas aspirin permanently inhibits COX-1, Thromboxane A2 (TXA2) production is reduced, ticagrelor, prasugrel and clopidogrel target the P2Y12 ADP receptor on platelets. The combination of low-dose rivaroxaban with aspirin is a prime example of dual pathway inhibition, which targets both thrombin production and platelet activation. Studies have demonstrated that reduced-dose dabigatran or rivaroxaban can significantly lower the risk of clinically significant bleeding while remaining as efficacious as full-dose VKAs in triple therapy, giving them safer alternatives for treating AF patients undergoing PCI. Further investigation into the safety and effectiveness of apixaban and edoxaban in this context is warranted.[13]

Stabilized Patients with ACS

The elevated risk of ischemia is probably due to factors promoting atherothrombosis that aren't affected by suppressing thromboxane A2 or inhibiting P2Y12. Thrombin is the primary suspect because it initiates the process of converting fibrinogen to fibrin and highly stimulates platelets. This view is reinforced by research showing that patients with ACS treated with aspirin and on Unfractionated Heparin (UFH) or Low-Molecular-Weight Heparin (LMWH) suffered fewer ischemia episodes. Based on a meta-analysis of six studies, hospitalized patients with unstable angina may have lower mortality and heart attack risks (Relative Risk, 0.67; 95% Confidence Interval, 0.44-1.02) when utilizing therapeutic doses of UFH in addition to aspirin. Therapeutic UFH has been shown to be no more effective than full-dose LMWH in preventing recurrent ischemic events in patients with ACS. The risk of bleeding when using LMWH in addition to aspirin was equivalent to that of UFH.[14]

In individuals with ACS, therapeutic UFH has not been demonstrated to be any more successful in avoiding recurrent ischemia episodes than full-dose LMWH. When using LMWH together with aspirin, the bleeding risk was the same as with UFH.

In the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) study, 11378 patients with non-ST-segment-elevation Acute Coronary Syndromes (ACS) were randomly assigned to receive full-dose enoxaparin (1 mg/kg bid) or fondaparinux (2.5 mg qd) for a mean of 6 days.29 Fondaparinux almost prevented significant bleeding when administered at a dosage less than full-strength enoxaparin (HR, 0.52; 95% CI, 0.44-0.61). Furthermore, despite having lower anti-FXa levels than enoxaparin (HR, 1.01; 95% CI, 0.90-1.13), fondaparinux was just as effective. The considerable reduction in mortality observed with fondaparinux raised the possibility of a net therapeutic benefit.[15]

Enhanced Atherothrombosis Prevention with Combined Low-Dose Rivaroxaban and Aspirin Therapy

At the locations where atherosclerotic plaque ruptures, thrombus formation and growth must be inhibited by blocking both platelet activation and the coagulation system. As such, addressing both routes in a therapeutic strategy is expected to be more successful than focusing on just one. Vitamin K Antagonists (VKAs) have been examined in conjunction with aspirin to enhance antithrombotic therapy for individuals with Coronary Artery Disease (CAD) or Peripheral Arterial Disease (PAD). For example, using aspirin together with normal-intensity warfarin (INR 2.0-3.0) decreased ischemic stroke by 54% and recurrent MI by 44% in individuals who had Myocardial Infarction (MI). Nonetheless, a 2.5-fold rise in significant bleeding offset these advantages. However, in patients with PAD, neither aspirin nor aspirin combined with usual-intensity warfarin significantly reduced Major Adverse Cardiovascular Events (MACE).[16] Still, it did cause a 3.4-fold rise in potentially fatal hemorrhage. For patients with stable CAD or PAD, low-intensity warfarin is therefore considered useless and the usual-intensity warfarin plus aspirin combo offers little help because of the higher risk of potentially fatal hemorrhage.

A recent trial called COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) found that low-dose rivaroxaban combined with aspirin is more beneficial than either drug alone. According to research conducted on animals and *in vitro*, aspirin blocks thromboxane A2-mediated platelet activation, which increases rivaroxaban's inhibitory action on thrombin production. This might lead to the usage of rivaroxaban at lower, less dangerous levels. There were 27,395 participants with stable PAD or CAD in the COMPASS study. They were then randomly assigned to receive 2.5 mg of rivaroxaban twice daily in addition to aspirin, 5 mg of rivaroxaban twice day alone, or 100 mg of aspirin once day. Relative risk was determined to be 0.84 (95% CI: 0.73-0.96), which is higher for low-dose rivaroxaban+aspirin when it comes to preventing MACE than for rivaroxaban alone. In comparison to aspirin alone, there were similar increases in severe bleeding (HR, 1.70; 95% CI, 1.40-2.05 and HR, 1.51; 95% CI, 1.25-1.84), primarily in the gastrointestinal tract, with the combined regimen. For controlling such bleeding,

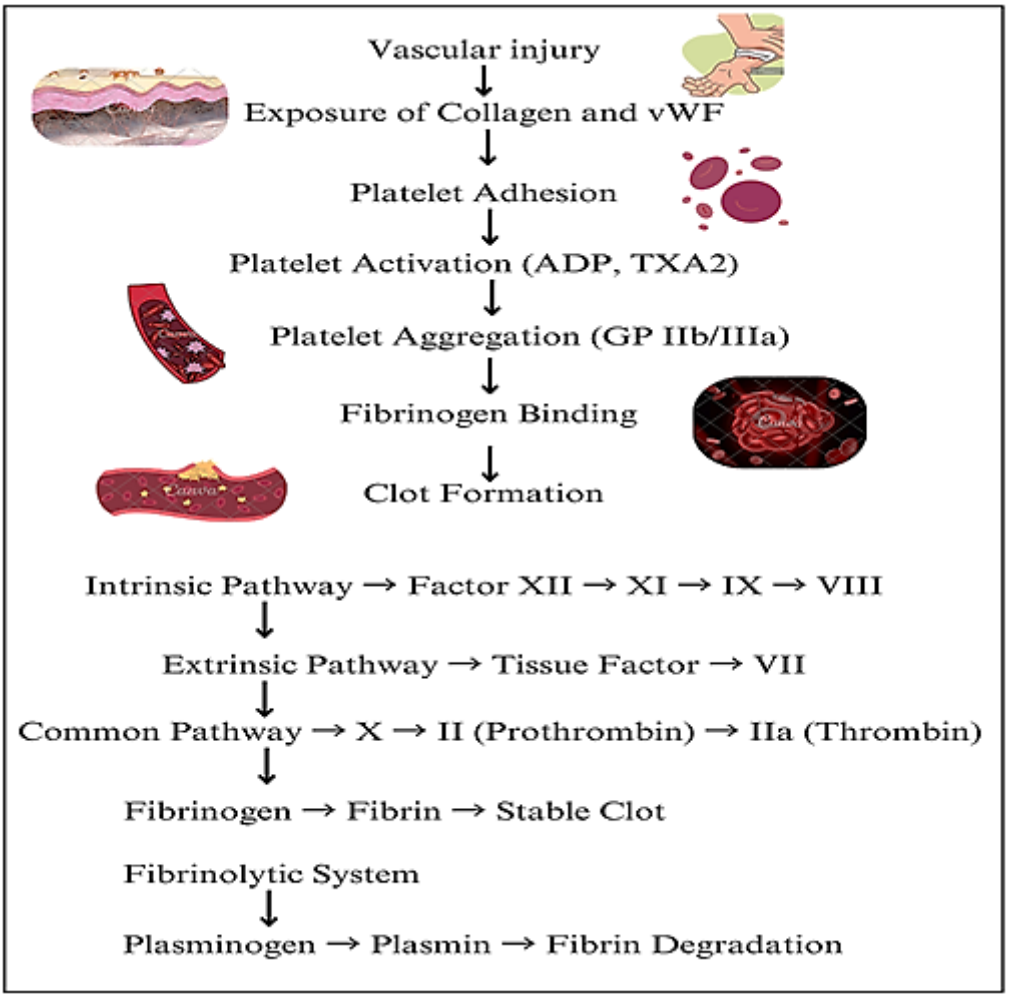

Figure 1: Coagulation Cascade.

standard therapies such as acid-suppressive drugs and endoscopic procedures are advised.[17]

By generating minimum peak and trough levels (geometric means of 47 ng/mL and 9.2 ng/mL, respectively), rivaroxaban 2.5 mg twice a day lessens the need for reversal medications such prothrombin complex concentrates or Andexanet alfa. High-dose rivaroxaban with aspirin prevents atherothrombosis better than either drug alone, according to the COMPASS study's findings. This is a significant improvement above combination treatment utilizing VKAs. Table 2 summarizes the key strategies of hemostatic and anti-thrombotic agents, outlining their therapeutic target, types of studies provide overview to support informed decision-making in managing thrombotic and bleeding disorders and clinical implications.

ADVERSE EVENT AND ITS MANAGEMENT

Bleeding commonly occurs as a complication in patients receiving either Oral Anticoagulation (OAC) or antiplatelet therapy. Dual Antiplatelet Therapy (DAPT), which includes aspirin and a P2Y12 inhibitor, is still the recommended course of treatment for patients getting Percutaneous Coronary Intervention (PCI) with stenting and those with Acute Coronary Syndrome (ACS), despite the potential for bleeding. Furthermore, choosing stronger P2Y12 inhibitors over clopidogrel like ticagrelor and prasugrel increases the risk of bleeding. There are several categories for varying degrees of bleeding issues, including life-threatening, moderate, severe and mild bleeding.[18]

Antithrombotic therapy after bleeding requires careful consideration, depending on the severity of the bleeding episode. According to guidelines published by the European Society of Cardiology (ESC) as shown in Figure 2, antithrombotic medicine should be administered continuously in minor bleeding situations that do not necessitate medical attention. It may be appropriate to move from dual treatment, which consists of clopidogrel and Oral Anticoagulant (OAC), to triple therapy, which comprises of OAC plus Dual Antiplatelet Therapy (DAPT). In order to maintain hemodynamic stability, moderate bleeding, which is characterized by a large blood loss (≥2 mmol/L hemoglobin), must be carefully monitored and managed over time. Hospitalization is necessary for a patient who is hemodynamically stable when there is severe bleeding, defined as blood loss of more than 3 mmol/L hemoglobin. Abrupt discontinuation of all antithrombotic drugs is necessary in cases of life-threatening bleeding, such as acute gastrointestinal bleeding or cerebral hemorrhage.[19]

One common side effect of antithrombotic treatment is gastrointestinal bleeding. Dual antiplatelet medicine can raise the risk of gastrointestinal bleeding and increase the likelihood of diverticular bleeding when low-dose aspirin is used. When taking clopidogrel and more contemporary P2Y12 antagonists, including ticagrelor and prasugrel, there is an increased risk of gastrointestinal bleeding and ulcer. Although warfarin causes

Table 2: Strategies of Hemostatic agents.

Characteristics	Explanation
AF, ACS and CAD	ACS and CAD are common in AF patients, DAPT is recommended for stent thrombosis, although anticoagulants are superior for preventing stroke.
Triple therapy in AF-PCI	The standard course of treatment involves VKA and DAPT, however there is a 12% yearly chance of bleeding.
WOEST Trail	Triple therapy (Aspirin+Clopidogrel+VKA) had a 6.5% bleeding rate compared to 12.7% for dual therapy (Clopidogrel+VKA). Currently, guidelines states that dual therapy (DOAC+Clopidogrel) is preferred agents.
PIONEER-AF Study	Rivaroxaban (15 mg+clopidogrel) and (2.5 mg BID+Aspirin+Clopidogrel) was compared to showed similar efficacy to warfarin-based triple therapy.
REDUAL-PCI Study	The bleeding risk was lower with dual therapy (dabigatran+P2Y12 inhibitors) than with VKA-based triple therapy and there was no increase in MACE.
OASIS-5 Study	The comparison between Fondaparinux (2,5 mg QID) versus Enoxaparin (1 mg/kg BD); the result shows fondaparinux reduced major bleeding by 48% and maintaining efficacy.
COMPASS Trail Study	The study shows the comparison between Rivaroxaban 2.5 mg BD and Rivaroxaban+Aspirin decreased MACE. Acid suppressants were used to control the gastrointestinal bleeding.
ACS Stabilization	Thrombin plays a key role in bleeding events. UFH & LMWH with aspirin lower the risk of ischemia but have similar bleeding risks.
Atherothrombosis Prevention	It is more effective to prevent platelet coagulation and activation. Warfarin+Aspirin reduces the risk of stroke and MI but increased risk of major bleeding.
Clinical Implications	Low dose Rivaroxaban+Aspirin is safer and more effective than warfarin-based regimens for CAD/PAD patients.

less harm to the stomach mucosa when combined with aspirin or clopidogrel, it significantly raises the risk of gastrointestinal hemorrhage. Warfarin-related gastrointestinal side effects are more prevalent with direct thrombin inhibitors like dabigatran than they are with factor Xa inhibitors like rivaroxaban, apixaban and edoxaban.

The management of bleeding during antithrombotic therapy involves specific strategies. When using Vitamin K Antagonists (VKA), patients who have minor bleeding should wait to take their next dosage until their INR falls below the recommended therapeutic range. It is recommended to skip one dosage of Novel Oral Anticoagulants (NOACs). Intravenous vitamin K (5-10 mg) is advised for VKA users in situations of significant bleeding, however it takes 4-6 hr to start working. If the last dose was taken within 2-4 hr, charcoal may be used to treat bleeding associated to NOACs. Time is of the essence in this case. Individuals using dabigatran can require dialysis. For individuals with severe bleeding problems, concentrates of four-factor prothrombin complex (4F-PCC; 25-50 U/kg) and fresh frozen plasma may be utilized. The particular antidote can be substituted with 4F-PCC if NOACs are not available. Dabigatran can be reversed with 5 mg of intravenous adrenaline.[20]

Gastrointestinal bleeding management involves discontinuing oral anticoagulation during moderate episodes and resuming therapy after 7-15 days. For secondary prophylaxis, in situations of lower gastrointestinal bleeding, aspirin should be maintained. Aspirin should be used as normal during the seven-day P2Y12 inhibitor break during dual antiplatelet therapy if the patient has Acute Coronary Syndrome (ACS) or has had coronary stent placement. In the event of upper gastrointestinal hemorrhage, intravenous Proton Pump Inhibitors (PPI) are advised, with a switch to oral PPI upon discharge. VKAs can be prevented by using certain hemostatic drugs, such as Vitamin K (both K1 and K2). Concentrates of prothrombin complex and recombinant activated factor VII are used in more severe instances, albeit the latter is not advised because of the possibility of arterial thromboembolic events.[21]

Specific hemostatic agents play a crucial role in managing bleeding complications associated with antithrombotic therapy. Vitamin K, including both Vitamin K1 (phytonadione, Phytomenadione) and Vitamin K2 (menaquinone), is essential for counteracting the effects of Vitamin K Antagonists (VKAs). Vitamin K levels can be restored by intravenously or orally administering these vitamins, which are naturally found in food and generated by gut flora. A dosage of 5-10 mg is advised to counteract the effects of VKAs in patients who are suffering significant bleeding, have a noticeably raised International Normalized Ratio (INR), or have liver disease.[22]

When it comes to warfarin-related cerebral bleeding, plasma transfusion is a less ideal option for an instantaneous reversal of anticoagulation due to its extended average correction time of around 30 hr. Made from human plasma, Prothrombin Complex Concentrates (PCC) are concentrated versions of the vitamin K-dependent coagulation components (II, VII, IX and X) that offer a more efficient solution. After processing, they are lyophilized. VKAs are not reversed by PCCs; instead, DOACs (Direct Oral Anticoagulants), especially dabigatran, are reversed by PCCs. This is particularly true for both non-activated PCC and activated PCC (APCC).

The original purpose of recombinant activated factor VII, or rFVIIa (NovoSeven®, NovoNordisk, Denmark), was to control bleeding in hemophiliacs undergoing coagulation factor inhibitor therapy. However, because of the high risk of arterial thromboembolic events connected to its administration, its usage is generally not advised.[23]

MULTI-DISCIPLINARY APPROACHES TO THERAPY OPTIMIZATION OR PATIENT-CENTERED CARE

Antithrombotic therapy is essential for patients with Acute Coronary Syndrome (ACS), Chronic Coronary Syndrome (CCS) and those undergoing revascularization procedures like Percutaneous Coronary Intervention (PCI) and Coronary Artery Bypass Grafting (CABG) in order to prevent recurrent thrombotic

EUROPEAN SOCIETY OF CARDIOLOGY (DAPT Guidelines)	
Trivial Bleeding	In mild bleeding continue DAPT
Moderate Bleeding	≥ 2mmol/L Hb loss
Severe Bleeding	≥ 3mmol/L Hb loss

Figure 2 : European Society of Cardiology.

and ischemic events. However, albeit to differing degrees, these treatments also raise the risk of bleeding. Following PCI with Drug-Eluting Stents (DES), dual antiplatelet therapy, or DAPT, remains the cornerstone. The ratio of thrombosis risks to bleeding dangers affects the length and severity of DAPT. High Bleeding Risk (HBR) affects nearly 40% of patients requiring DAPT post-PCI, leading to considerations for reducing DAPT duration or de-escalating therapy to mitigate bleeding risks. Achieving an appropriate balance between bleeding and thrombosis risks while maintaining antithrombotic efficacy presents practical challenges.[24]

The management of CAD has evolved with the use of better pharmacological interventions, such as optimized statin medication and the clinical use of DES with antithrombotic properties, which has decreased the number of thrombotic and ischemic events that follow PCI. Nevertheless, a significant portion of HBR patients were excluded from earlier DES clinical trials due to their inability to endure prolonged DAPT. Trials like the LEADERS FREE have been designed to evaluate novel DES tailored for HBR patients, addressing the challenge of managing DAPT in those with bleeding complications, particularly as the elderly population with multiple health conditions rises.

Ticagrelor, prasugrel and clopidogrel are the P2Y12 inhibitors that are currently prescribed in clinical settings. Despite being the conventional DAPT regimen, clopidogrel has many drawbacks, including a delayed beginning of action and interpatient variability in antiplatelet response. Genotype-guided selection of P2Y12 inhibitors may be advantageous as the CYP2C19 genotype impairs hepatic biotransformation, which reduces the effectiveness of clopidogrel. According to Claassens *et al*., decreasing bleeding risk without raising the risk of thrombotic events is possible with a CYP2C19 genotype-guided strategy. Nonetheless, AHA/ACC, ESC and JCS guidelines have recently moved away from routine genetic testing due to mixed evidence regarding its benefits.[25]

Some of clopidogrel's limitations are addressed by ticagrelor and prasugrel. Although there was an increase in bleeding, the TRITON TIMI 38 study showed that prasugrel was superior than clopidogrel in lowering cardiovascular events including stent thrombosis. In the PRASFIT-Elective trial, a lower dosage of prasugrel was tested for Japanese patients with coronary artery disease; this dose was shown to be just as safe and effective as the lower dose used in the TRITON-TIMI 38 study. While ticagrelor shown minimal therapeutic effectiveness, prasugrel was reported to be efficacious with comparable bleeding events and fewer thrombotic events in the ISAR-REACT 5 study.[26]

For patients requiring long-term anticoagulation due to artificial heart valves, systemic thromboembolism, or Atrial Fibrillation/Flutter (AF), the combination of DAPT with Oral Anticoagulants (OACs) is recommended. Approximately 20-30% of these individuals additionally need PCI for ischemic heart disease. Triple Therapy (TT) is advised for patients who are contraindicated for anticoagulation, despite the fact that it might result in excessively severe bleeding, with rates ranging from 2.2% in the first month to 4-12% in the first year. Due to elevated bleeding risks, recommendations place a strong emphasis on TT duration reduction.[27]

Most trials on TT involved warfarin as the OAC, with guidelines suggesting an INR goal of 2 to 2.5, though this is not strongly supported by clinical data. Data on Newer Oral Anticoagulants (NOACs) in TT is limited. Compared to DAPT alone, the ATLAS-ACS-TIMI 46 study discovered that adding regular 20 mg rivaroxaban to DAPT increased bleeding but decreased thrombotic events. A 2.5 mg dose of rivaroxaban given twice daily decreased cardiovascular events without increasing the

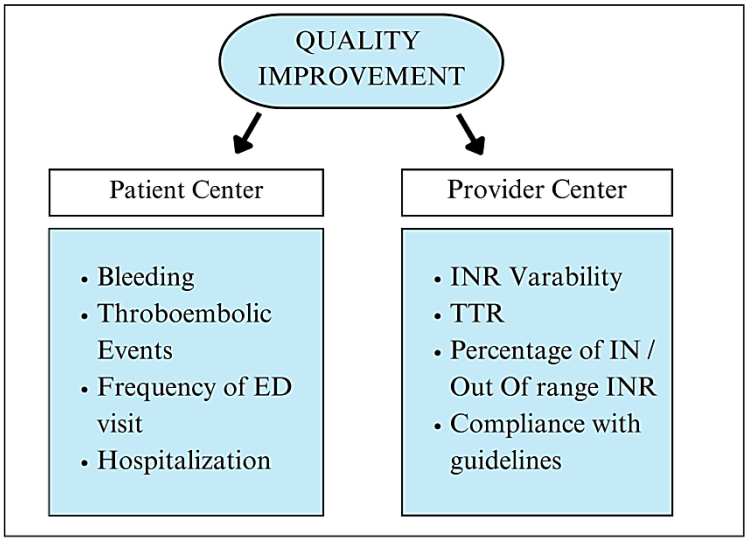

Figure 3: Quality Improvement.

risk of catastrophic bleeding despite the fact that its efficacy in preventing stroke in patients with atrial fibrillation is uncertain.

The APPRAISE study did not show benefit for apixaban in ACS and resulted in increased bleeding, while dabigatran also increased bleeding when added to DAPT. European guidelines recommend lower doses of NOACs for TT, aligning them with warfarin. The PIONEER AF PCI study showed rivaroxaban as effective as warfarin with less bleeding and ongoing trials like AUGUSTUS will further evaluate apixaban and rivaroxaban in this context.[28]

CHALLENGES IN THERAPY OPTIMIZATION

Antithrombotic therapy for Myocardial Infarction (MI) faces several challenges. Balancing the risks of bleeding and ischemia with Dual Antiplatelet Therapy (DAPT) is difficult, particularly when extending DAPT beyond 12 months, which increases bleeding risks. Choosing the optimal duration of DAPT, possibly transitioning to P2Y12 monotherapy for high bleeding risk patients, requires careful consideration, with tools like the DAPT score system offering guidance. Balancing the risks of bleeding and ischemia while using Direct-Acting Oral Anticoagulants (DOACs) with antiplatelet medication can be difficult, particularly in individuals who also have atrial fibrillation.[14] This equilibrium is made more difficult by new antithrombotic drugs, necessitating constant changes. In the case of Intracerebral Hemorrhage (ICH), managing bleeding and hematoma expansion is complicated by the lack of effective antidotes for new anticoagulants. For neonates, the immature hemostatic system and increased bleeding risks require careful management with blood products and a better understanding of neonatal hemostasis. Recurrent stroke treatment involves selecting appropriate antithrombotic agents based on the cause of ischemia while managing bleeding risks.[29]

QUALITY IMPROVEMENT INITIATIVES AND OUTCOME MEASURES

The strengths and possible problems of any system of coordinated care delivery may be evaluated using a quality-of-care measure. It is possible to classify patient-centred, provider-or process-focused key outcomes for quality improvement indicates as shown in Figure 3. Blood and thromboembolic events are examples of patient-centred outcomes. Included in the frequency of ER visits and hospital stays. The majority of the results (e.g., following procedures and responding quickly to laboratory data that deviates from the target range, including TTR, INR fluctuation, percentage of in/out of range INR readings and percentage of missing INR) were related to the process or the provider. Six centres came together to create the Michigan Anticoagulation Quality Improvement Initiative (MAQI2), which aims to improve the quality of anticoagulation management services offered in Michigan.[30]

Anticoagulation quality improvement initiatives are designed, implemented and reported using MAQI2. The project started in 2008 and involves routine in-person meetings with managers, employees and medical directors to discuss general and site-specific metrics. Effective treatment of anticoagulation can be achieved with direct oral anticoagulants such as apixaban, dabigatran, rivaroxaban and edoxaban; no dosage adjustments, regular monitoring, or interactions with other drugs or foods are necessary. There is a considerable danger of bleeding when these medications are used inappropriately.[31]

The ACCP guidelines serve as a cornerstone for ensuring top-notch management of anticoagulation care. Moreover, the Anticoagulation Forum provides a wealth of carefully curated resources for overseeing the use of warfarin and other anticoagulants. These resources encompass a variety of tools aimed at delivering superior anticoagulation care, along with an array of educational materials designed to empower patients. Anticoagulation physicians are able to evaluate their own performance and indicate problems that require focused treatments by participating in quality improvement initiatives. Four data points were provided most frequently: the mean warfarin dose, the percentage of samples in range, the mean INR and the percentage of time spent in range. Warfarin dose changes are likely to occur only when there is a problem with the INR measurements; the first three signs are related to therapeutic control. In order to monitor the INR findings and dosage recommendations, at least two outcome measures must recorded.[32]

EDUCATION AND TRAINING IN HEMOSTASIS AND THROMBOSIS CARE

One of the most important issues in enabling patients to self-manage thrombosis and hemostasis diseases is patient education. Effective anticoagulation education requires in-person communication with a qualified specialist who makes sure the patient is aware of the dangers associated with the medication, the necessary safety measures and the requirement for regular follow-up. Suitable education decreases the rate of hospital admissions and readmissions, enhance patient adherence to prescribed medication (dosage and frequency) and lower the incidence of undesirable drug side effects and interactions, follow-up appointment attendance and use of adjunct measures like compression stockings or diet changes. Patient education about the possible risks of using anticoagulants is usually provided as standard treatment and is stressed in a variety of healthcare settings, such as community pharmacies and ambulatory care centers.[33]

STEWARDSHIP

The therapeutic window for Hemostatic and Antithrombotic (HAT) medicines is limited, needing careful monitoring and dosage titration in order to effectively treat or prevent thrombosis without causing bleeding episodes. These medications have a high incidence of adverse effects because to improper patient selection, dosage and monitoring. They need to be closely maintained and constantly observed with extreme caution. These medications can have a substantial cost impact on health systems when they are misused or administered incorrectly. Particularly expensive are coagulation factor preparations and intravenous Direct Thrombin Inhibitors (DTIs). The HAT Stewardship program was created for these patients by the Department of Pharmacy Services and the Division of Hematology in order to optimize the availability of antithrombotic and hemostatic drugs.[34]

A stewardship program is an organized, effective and sustained system-level endeavor that aims to eliminate avoidable adverse events and produce optimum wellness outcomes.

In October 2013, the Hematologist Medical Director established the HAT Stewardship team, which consists of one pharmacist and inpatient hematology attending doctors. This signified the start of the HAT Stewardship program. Anticoagulant Stewardship refers to a well-coordinated, effective and enduring systemic effort aimed at attaining the best possible health outcomes related to anticoagulant use while reducing preventable Adverse Drug Events (ADEs).

Anticoagulation stewardship promotes patients in making decisions that improve their mental, physical and emotional well-being in order to enhance person-centred treatment and anticoagulant management. Reductions in medication-drug interactions, bleeding incidents, hospital readmissions, duration of stay and other healthcare costs are linked to anticoagulation stewardship.[35]

The Figure 4 describes the Seven Core Elements are designed to enhance the systematic administration of anticoagulants across various healthcare environments, aiming to ensure safe and patient care.

Ensure administrative leadership commitment

In hospital settings, the commitment of administrative leadership is required to establish a culture of accountability, education and adherence to evidence-based practices for antithrombotic treatment.

Healthcare administrators must commit administrative leadership by providing the required financial, technological and human resources to support antithrombotic stewardship. It is important for leaders to promote values regarding Anticoagulation Stewardship by continually positioning ADEs associated with anticoagulation as a serious threat to patient safety and stewardship as an important corporate effort. Leadership commitment generates revenue stams, impacts more significant organizational change, wins over multi-disciplinary support and permits ongoing development in an ever-changing setting.[36]

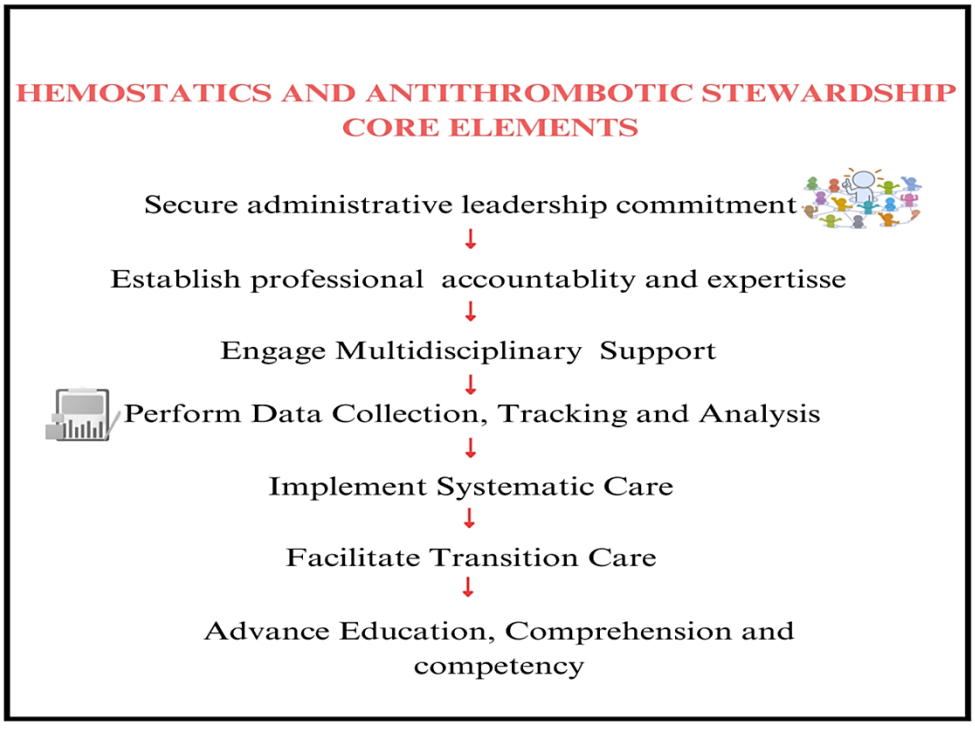

Figure 4: Hemostatics and Antithrombotic Stewardship Core Elements.

Establish Expertise and Professional Accountability

Establishing an anticoagulation stewardship program involves professionals who have the responsibility and give knowledge to create, administer and assess stewardship actions on a daily basis. Choosing a leader who is responsible for program results is one of the main components of ASP. The benefits of an anticoagulation service run by pharmacists have been the subject of several studies. Research indicates that the provision of optimum dosage, education, medication review and reconciliation by a pharmacist working in an ASP can have a favourable effect on adverse event rates, drug-drug and drug-food interactions and patient safety. Anticoagulation Stewardship programs have the potential to augment organizational goals, enlist crucial stakeholders, carry out quality enhancement endeavours and promote the safe administration of anticoagulants.[37]

Engage Multidisciplinary Support

The multidisciplinary team consists of clinical (e.g., medical, surgical, nursing, pharmacy, nutrition services and laboratory) and nonclinical departments (e.g., risk management, patient safety, quality, data analytics and IT), as well as patient representatives. Hospitals may guarantee that patients receive the best care possible and avoid antithrombotic adverse events by forming multidisciplinary ASP groups with members from a range of professions. These committees must to get together frequently to discuss and offer guidance on stewardship projects.[38]

Perform Data Collection, Tracking and Analysis

Effective data collection, tracking and analysis are important components of establishing a successful Anticoagulation Stewardship program. With strong processes for gathering and analyzing anticoagulation-related data in place, organizations can pinpoint areas needing improvement in anticoagulant care practices, determine key areas for action, address these improvement opportunities and promote for additional resources.[39]

Implement Systematic Care

To maintain the safety and quality of anticoagulation management procedures, systematic care necessitates the implementation of long-term, efficient and evidence-based system-wide interventions. Systematic anticoagulation care emphasizes evidence-based practices, person-centeredness and integrated systems and clinical workflows for prescribing, dispensing and maintaining anticoagulants. Included are clinical decision support, clinical pharmacy programs, guidelines, protocols, constraints on formularies and procedures. Programs and training materials are also offered. The strategies included anticoagulation therapies to maximize HIT management, computerized clinical decision support systems to improve patient safety in the inpatient environment and drug surveillance for inpatients undergoing anticoagulant treatment.[40]

In systematic care, three methods are employed. Initially, all ASP participants should be up to date on the latest findings and research on anticoagulation safety and management. The approaches employed should be grounded in evidence. Second, the program design and activities should revolve around the patient and the ASP should take the patient's perspective into account. Third, interventions should be completely integrated into clinical practices and organizational decision-making, with metrics focused on the system level to optimize the chances of ASP sustainability and success. Systematic anticoagulation stewardship implementation can lead to improved interdisciplinary involvement, evidence-based treatment, real-time feedback and quality improvement initiatives.[41]

Facilitate Transitions of Care

Antithrombotic drug mistakes can occur during treatment transitions, such as from inpatient to outpatient settings. To minimize such mistakes, the influence of inpatient pharmacist-directed anticoagulation services on care transitions. It was cost-effective to use their transfer of care service. All patients are more vulnerable to ADEs, including bleeding, stroke and VTE, as well as clinical management errors and mistakes when there are insufficient care transitions, especially those on anticoagulants.

Effective care transitioning organizations are able to facilitate continuous physician-to-physician communication, provide transparent patient-provider channels and promote the continual use of advised medicines.[42]

Advance Education, Comprehension and Competency

Ensuring evidence-based recommendations and anticoagulation best practices are followed and patients, physicians and other health care professionals possess the information and abilities required for optimal antithrombotic treatment. Education served as an important approach for patients, delivered by pharmacists and a multidisciplinary team.[43]

To get optimal understanding and knowledge, learning resources must be provided in several forms (such as written, audio and visual), quickly accessed and adjusted to physicians' schedules. Moreover, patient education materials must to be visually appealing and suitable for various languages and reading levels. Regular education for both patients and Healthcare Professionals (HCPs) is essential to maintain ongoing comprehension.[44]

CONCLUSION

Optimizing hemostatic and antithrombotic therapies requires a multifaceted stewardship approach to balance efficacy and safety, minimize adverse events and enhance patient outcomes. Comprehensive strategies should include individualized risk assessment, evidence-based treatment protocols and

multidisciplinary collaboration to ensure precise dosing, timely intervention and appropriate monitoring. Incorporating advanced diagnostic tools, patient education and integration of clinical decision support systems can further enhance therapeutic effectiveness. Regular review and adherence to updated clinical guidelines are essential to mitigate risks such as bleeding or thrombotic complications. Emphasizing education for healthcare providers and patients ensures better understanding and adherence to prescribed therapies. Additionally, fostering a culture of continuous quality improvement within healthcare systems supports the refinement of treatment strategies. By prioritizing a patient-centred approach, leveraging innovation and ensuring robust monitoring, stewardship programs can successfully optimize hemostatic and antithrombotic therapies, ultimately improving clinical outcomes.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

ACC: American College of Cardiology; **ACCA:** Acute Cardiovascular Care Association; **ACCP:** American College of Chest Physician; **ACS:** Acute Coronary Syndrome; **ADE:** Adverse Drug Event; **ADP:** Adenosine diphosphate; **AF:** Atrial Fibrillation; **AHA:** American Heart Association; **APCC:** Activated prothrombin complex concentrate; **ASP:** Anticoagulant Stewardship Program; **ATLAS ACS-TIMI:** Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction; **AUGUSTUS:** Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; **CABG:** Coronary artery bypass graft surgery; **CAD:** Coronary Artery Disease; **CCS:** Chronic coronary syndrome; **CHADS 2:** Congestive heart failure, Hypertension, Age > 75 years, Diabetes CI Contraindication; **COMPASS:** Cardiovascular Outcomes for People Using Anticoagulation Strategies; **COX:** Cyclooxygenase; **DAPT:** Dual antiplatelet therapy; **DES:** Drug-eluting stents; **DOAC:** Direct oral anticoagulants; **DTI:** Direct thrombin inhibitors; **ESC:** European Society of Cardiology; **HAT:** Hemostatic and Anti-thrombotic therapy; **HBR:** High bleeding risk; **HCP:** Health Care Professionals; **HIT:** Heparin induced Thrombocytopenia; **IT:** Information Technology; **ISTH:** International Society on Thrombosis and Hemostatic; **INR:** International normalized ratio; **ISAR-REACT:** Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment; **LMWH:** Low Molecular Weight Heparin; **MACE:** Major adverse cardiac events; **MAQI 2:** Michigan Anticoagulation Quality Improvement Initiative; **MI:** Myocardial Infarction; **NOAC:** Non-Vitamin K Antagonist Oral Anticoagulants; **NSAID:** Non-Steroidal Anti-inflammatory drug; **OAC:** Oral anticoagulant; **OASIS 5:** Fifth Organization to Assess Strategies in Ischemic Syndromes; **PAD:** Peripheral arterial disease; **PCC:** Prothrombin complex concentrates; **PCI:** Percutaneous coronary intervention; **PIONEER AF:** Prevention of Bleeding in Patients with Atrial Fibrillation; **PIONEER AF-PCI:** Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; **PPI:** Permanent pacemaker implantation; **PRASFIT:** Prasugrel Compared to Clopidogrel for Japanese Patients; **RE-DUAL-PCI:** Randomized Evaluation of Dual Antithrombotic Therapy Patient Undergoing Percutaneous Coronary Intervention; **STEMI ST:** Segment Elevation Myocardial Infarction; **TRITON TIMI:** Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in myocardial infraction; **TT:** Thrombin Time; **TXA2:** ThrombaxaneA2; **UFH:** Unfractionated Heparin; **VKA:** Vitamin K Antagonist; **VKORC-1:** Vitamin K epoxide reductase complex subunit 1; **VTE:** Venous thromboembolism; **WOEST:** What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation undergoing revascularization.

SUMMARY

The introduction to the functions of hemostatic and antithrombotic drugs in the treatment of thrombotic and bleeding diseases, this thorough study into important facets of these medications. In order to comprehend the equilibrium between coagulation and fibrinolysis, the hemostatic system is studied. Anticoagulants, antiplatelets and thrombolytics are highlighted in a thorough review of antithrombotic agents, along with strategies of antithrombotic therapies for individualized treatment plans. The treatment of adverse events is discussed, with a focus on early detection and action. It emphasizes the value of multidisciplinary methods to therapy optimization and encourages cooperation across medical teams. These includes discussion of the current difficulties in therapy optimization, such as striking a balance between safety and efficacy. By using evidence-based techniques, quality improvement programs and outcome measures seek to improve patient care. Hemostasis and thrombosis care education and training promotes proficiency and creativity. Finally, the stewardship of antithrombotic and hemostatic drugs guarantees proper use, guided by the seven fundamental components that serve as the cornerstone for maximizing benefits and lowering risks.

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