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A review on Patient Compliance and Response to Anticoagulant Therapy in Cardiovascular Disease Management

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ABSTRACT

Cardiovascular diseases (CVDs) remain a leading cause of global morbidity and mortality, with anticoagulant therapy playing a critical role in preventing thromboembolic events. Despite the efficacy of these treatments, patient compliance remains a significant challenge, influencing clinical outcomes and healthcare costs. This review examines the factors affecting adherence to anticoagulant therapy, the impact of novel anticoagulants on compliance rates, and the clinical consequences of non-adherence. By assessing existing literature and patient case studies, this article highlights barriers to optimal treatment adherence and proposes strategies to enhance patient compliance and therapeutic efficacy in cardiovascular disease management.

Keywords: *Anticoagulant therapy, Patient adherence, Direct oral anticoagulants (DOACs), Therapeutic drug monitoring*

1. INTRODUCTION

1.1 Burden of Cardiovascular Diseases (CVDs) Requiring Anticoagulation

Globally, CVD is the primary cause of death [1, 2]. CVD was responsible for 18.6 million deaths in 2019 (33% of all fatalities), and by 2030 [3], it is expected to cause 24 million deaths annually [4]. Nearly 25% of all fatalities in England and Wales in 2019 were attributable to CVD [5,6]. In England, higher socioeconomic disparities among those under 75 have also been linked to premature death from CVD [7].

Anticoagulation is one potential preventive measure for people who are at high risk for heart attacks, strokes, deep vein thrombosis, or pulmonary embolism [8]. Anticoagulants work to stop blood clots from forming and the negative consequences of excessive clotting by targeting several locations along the coagulation cascade. Between January 2014 and August 2019, the number of anticoagulant prescriptions in primary care in England rose from 15 million to 33 million doses [9]. According to guidelines released by the National Institute for Health and Care Excellence (NICE), there are three primary categories of anticoagulants: direct-acting oral anticoagulants (DOACs; such as rivaroxaban), vitamin K antagonists (such as warfarin), and low molecular weight heparins (such as enoxaparin). Anticoagulants are known to be beneficial in treating CVD. For instance, in individuals with atrial fibrillation, adjusted-dose warfarin decreased stroke by 62% (95% CI = 48% to 72%) [10]. However, DOACs have been developed as a result of the limited therapeutic index and regular laboratory testing required with warfarin treatment [11]. One of the top three adverse medication responses that result in hospitalizations in England is bleeding related to warfarin treatment [11].

1.2 Role of Anticoagulants in CVD Management

One of the most important aspects of managing cardiovascular disease is anticoagulation. Acute coronary syndrome, percutaneous coronary intervention, atrial fibrillation, cardioversion, and cardiac valve replacement have all been treated using innovative anticoagulant techniques throughout the last ten years. Treating doctors must be informed on the best anticoagulation techniques for cardiovascular disease when new research supporting the use of anticoagulants becomes available. In this review, we highlight the advantages and disadvantages of using new anticoagulants in these situations while offering a succinct synopsis of the evidence bolstering current anticoagulation treatments [12].

1.2.1 ACUTE CORONARY SYNDROME ANTICOAGULATION

1.2.1.1 Acute coronary syndrome without ST elevation

Unstable angina (UA) and non-ST elevation myocardial infarction (NSTEMI) are both included in non-ST elevation acute coronary syndrome (NSTE-ACS). One The cornerstones of therapy for these disorders are antiplatelet and anticoagulant medications, which lower myocardial damage and delay or stabilize thrombus formation [13]. Guidelines for anticoagulation in NSTE-ACS and information contrasting the effectiveness of unfractionated, low molecular weight, and ultra-low molecular weight heparins in this context are included in the section that follows.

1.2.1.2 Current guidelines for NSTE-ACS anticoagulation

In addition to antiplatelet medication, the 2014 American Heart Association (AHA)/American College of Cardiology (ACC) recommendations provide a number of possibilities for anticoagulant therapy in patients with NSTE-ACS:

Unfractionated heparin, 60 IU/kg loading dose (maximum 4000 IU) followed by 12 IU/kg/h (maximum 1000 IU/h), and Enoxaparin, 30 mg loading dosage followed by 1 mg/kg every 12 hours Bivalirudin, 0.10 mg/kg loading dosage followed by 0.25 mg/kg/h (only for early invasive approach), or Fondaparinux, 2.5 mg daily [14].

The patient's entire management plan should be considered while selecting an anticoagulant treatment. Given their potential benefits in the event of mechanical difficulties during cardiac catheterization, intravenous anticoagulants with a shorter half-life, such UFH or bivalirudin, may be preferred in patients receiving early invasive management. Protamine sulfate may also counteract the anticoagulant effects of heparin products, making them an alternative for patients who are at high risk of bleeding; nevertheless, it is important to note the modest risk of allergic responses with protamine [15]. Although fondaparinux is recommended by the European Society of Cardiology (ESC) recommendations because it has been linked to a reduction in significant bleeding, its broad usage has probably been constrained by worries about an elevated risk of catheter-related thrombosis during PCI. Individuals on fondaparinux who have angiography additionally need to take an anti-IIa medication (either bivalirudin or UFH) for extra anticoagulation. However, fondaparinux could be better than other medications, particularly for people who aren't having angiography [16].

1.2.1.3 Antiplatelet and anticoagulant vs antiplatelet alone

Some, but not all, clinical studies have demonstrated a mortality advantage from using low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) in addition to antiplatelet medication (mostly aspirin, ASA). When comparing patients receiving both UFH and ASA to those getting ASA alone, a meta-analysis of six studies revealed a relative risk reduction of 0.67 in mortality and non-fatal MI, which was close to statistical significance (CI 95% 0.44-1.02; P = 0.06) [17]. Patients taking LMWH with ASA had substantially lower rates of recurrent angina, non-fatal MI, and urgent revascularization, according to a small research comparing LMWH and ASA to ASA alone [18]. Patients treated with LMWH plus ASA had a significantly lower risk of mortality or MI (1.7% and 4.7%, respectively, CI 0.20-0.68; P = 0.001) in a larger RCT comparing LMWH (dalteparin) and ASA to ASA alone. After 40 days, the 3% absolute risk decrease (65% relative risk reduction) was no longer maintained [19]. When compared to ASA alone, the relative effectiveness of the UFH or LMWH plus ASA therapy groups may be impacted by the varying concurrent ASA dosage employed in these studies, which ranges from 75 to 650 mg loading or daily dose.

1.2.1.4 Low-molecular-weight heparin with antiplatelet vs antiplatelet and unfractionated heparin

Clinical management of unstable angina and non-ST elevation myocardial infarction involves the use of both UFH and LMWH medications. More duration in the therapeutic range, less vulnerability to inactivation by activated platelets, and a decreased risk of heparin-induced thrombocytopenia are some of the benefits of LMWH therapy over UFH [20]. When paired with various antithrombotic regimens, these mechanistic benefits translate into a tendency toward LMWH medications being superior to UFH treatments, with varying effects on bleeding risk.

According to Cohen et al.'s multicenter randomized controlled trial ESSENCE, antithrombotic treatment with enoxaparin and ASA as opposed to UFH and ASA in patients with unstable angina and non-Q-wave myocardial infarction is linked to a statistically significant reduction in a composite of death, myocardial infarction, and recurrent angina at 14 and 30 days. However, LMWH anticoagulation was linked to a significant rise in small hemorrhagic episodes, mostly ecchymosis at the injection site. 8. Composite mortality, myocardial infarction, or urgent revascularization were significantly reduced at 8 (OR 0.83; 95% CI 0.69-1.00; P = 0.048) and 43 (OR 0.85; 95% CI 0.72-1.00; P = 0.048) days in the TIMI 11B study, which also compared LMWH to UFH in patients with NSTE-ACS [21]. According to a meta-analysis of many studies comparing LMWH with UFH, LMWH had a lower risk of MI, revascularization, and thrombocytopenia, but UFH and LMWH had a comparable risk of death, recurrent angina, and major or minor bleeding. 10.

LMWH seems to provide potential advantages for both invasively managed and high-risk individuals. In 746 high-risk patients with NSTE-ACS, INTERACT compared LMWH plus eptifibatide and ASA to UFH plus eptifibatide and ASA. The results showed that the LMWH group had a significantly lower risk of mortality or myocardial infarction after 30 days (5% vs. 9%, respectively; P = 0.031) [22]. There was a trend toward a decrease in death, MI, and refractory ischemia in the

enoxaparin treatment arm, which was not inferior to the UFH treatment arm, according to the A to Z study, a randomized, multicenter, open-label trial that compared enoxaparin, aspirin, and tirofiban to UFH, aspirin, and tirofiban. In a similar vein, SYNERGY demonstrated that enoxaparin was not inferior to UFH in 10 027 high-risk patients receiving early invasive treatment; enoxaparin was associated with a tendency toward lower mortality in patients with NSTE-ACS, but it also increased TIMI major bleeding (9.1% vs. 7.6%, P = 0.008) [23]. Because some patients who were assigned to enoxaparin also got UFH, crossover was blamed for some of the severe bleeding increases in this experiment. According to another small research, anticoagulation is significantly increased when UFH and LMWH overlap, which is underreported by conventional laboratory monitoring [24]. The ESC strongly advises avoiding moving patients with NSTE-ACS between LMWH and UFH once therapy has started due to this findings. Although there was no discernible difference in major bleeding events between treatment groups receiving enoxaparin and UFH, a subsequent systematic review of the aforementioned trials by Petersen et al. [25] revealed a significant decrease in composite death or myocardial infarction (10.1% vs. 11.0%; OR, 0.91; 95% CI, 0.83-0.99; NNT = 107).

1.2.1.5 Heparin with low molecular weight vs heparin with ultra-low molecular weight

Fondaparinux is a highly specific indirect factor Xa inhibitor and a synthetic pentasaccharide used parenterally. After nine days, there was no difference in mortality, myocardial infarction, or refractory ischemia between fondaparinux and enoxaparin in patients with NSTE-ACS, according to the results of the double-blind multicenter study OASIS-5 (HR 1.01; 95% CI 0.90-1.13, P = 0.007 for non-inferiority) [26]. Additionally, fondaparinux reduced major bleeding events significantly compared to enoxaparin (2.2% vs. 4.1%, HR 0.52; 95% CI 0.44-0.61; P < 0.001), which is probably what caused fondaparinux patients to have a significantly lower 30-day reduction in composite death, MI, stroke, and major bleeding risk compared to those on enoxaparin (9.5% vs. 11.7%, HR 0.81; 95% CI 0.7-0.93; P = 0.004) [27]. Alongside the decrease in severe bleeding, there were statistically significant reductions in big hematomas, vascular access site problems, and pseudoaneurysms that needed to be closed. Due to fondaparinux's long half-life, lack of reversibility, and requirement to administer additional UFH or bivalirudin at the time of angiography, its widespread use in NSTE-ACS patients who may undergo PCI has been limited. Notably, fondaparinux was linked to an increase in catheter-associated thrombosis in patients undergoing PCI (RR 3.59; 95%, CI 1.64-7.84; P = 0.001) [28]. However, it is still an option, particularly for individuals who are unlikely to get coronary angiography while in the hospital.

2. CLASSES OF ANTICOAGULANTS AND THEIR MECHANISMS

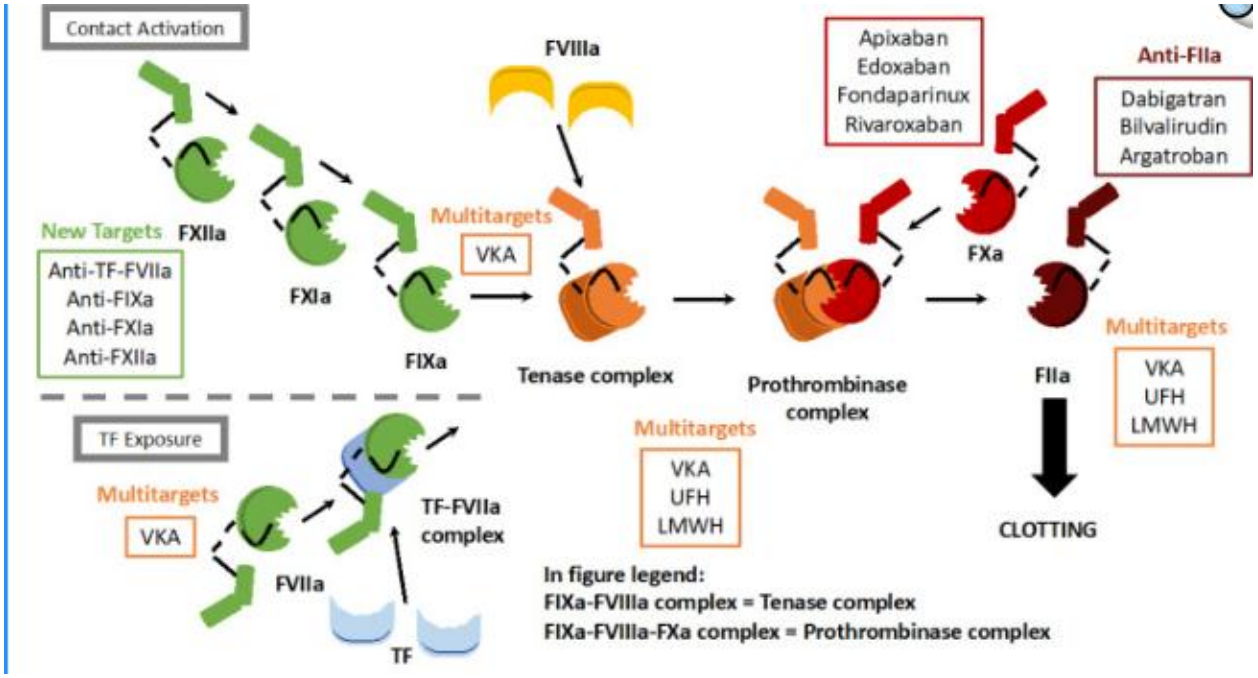
The first anticoagulant drugs to prevent VTE, unfractionated heparin and warfarin, were identified by serendipity in the early 20th century [6,7]. In the following years, these drugs have been optimized to prevent or treat VTE more efficiently. More recently, a novel generation of anticoagulant drugs has been introduced, which are designed to target coagulation factor IIa (thrombin) and coagulation factor Xa (FXa), two enzymes that are crucial for coagulation [30]. Depending on the medical indication, nowadays, physicians can prescribe different anticoagulant drugs that are best-suited for the needs of their patients. However, although anticoagulant drugs are effective in preventing VTE, they still have constraints in terms of maneuverability and associated hemorrhagic risk

Table 1: Classes of Anticoagulants and Their Mechanisms in Cardiovascular Disease Management

Class	Example Drugs	Mechanism of Action	Key References
Vitamin K Antagonists (VKAs)	Warfarin, Acenocoumarol	Inhibits vitamin K epoxide reductase, preventing γ-carboxylation of clotting factors II, VII, IX, X	[31]
Direct Thrombin Inhibitors	Dabigatran (DOAC)	Binds directly to thrombin (Factor IIa), blocking fibrinogen conversion to fibrin	[32]
Factor Xa Inhibitors (DOACs)	Rivaroxaban, Apixaban, Edoxaban	Directly inhibits Factor Xa, reducing thrombin generation	[33]
Low-Molecular-Weight Heparin (LMWH)	Enoxaparin, Dalteparin	Binds antithrombin III, enhancing inhibition of Factor Xa and thrombin	[34]
Unfractionated Heparin (UFH)	Heparin sodium	Activates antithrombin III to inhibit thrombin and Factor Xa (requires IV/SC administration)	[35]
Direct Factor XI/IX Inhibitors (Investigational)	Abelacimab, Osocimab	Novel targets to prevent thrombosis while minimizing bleeding risks	[36]

2.1. Unfractionated Heparin

Unfractionated heparin (UFH) was the first anticoagulant drug, discovered in 1916 by a medical student at Johns Hopkins University, Jay McLean, while studying the putative prothrombotic properties of dog liver and heart extracts [37]. Surprisingly, the compound, later named heparin (since it was identified in the dog's liver), demonstrated remarkably strong anticoagulant effects [12]. In the 1930s, several labs were able to purify UFH, and the compound was approved for clinical use. For the next couple of decades, UFH was used to prevent clotting in humans, without a real understanding of the mechanism of action [38]. It was not until the 1970s that it was discovered that UFH is a mixture of polymorphic polysaccharide chains obtained after the purification of vertebrate organs. These polysaccharide chains significantly enhance the activity of the major natural inhibitor of coagulation, antithrombin, which in healthy individuals accounts for the majority of all natural anticoagulation [14]. Antithrombin is a serine protease inhibitor that primarily antagonizes thrombin and FXa, two pivotal actors within the coagulation cascade [15] (Figure 1). Once antithrombin binds to thrombin or FXa, they form a complex that is rapidly degraded by the circulation [16]. The interaction of UFH with antithrombin is mostly mediated by a unique pentasaccharide sequence that is randomly distributed along the polysaccharide chains [39]. Since UFH accelerates the mode of action of antithrombin by approximately 1000 times, it functions as a highly efficient anticoagulant drug



Anticoagulants and their targets within the coagulation cascade. The coagulation cascade consists of three parts: the tissue factor (TF) pathway, the contact activation pathway, and the common pathway. Currently used anticoagulants target primarily coagulation factors from the common pathway: FXa (apixaban, edoxaban, fondaparinux, and rivaroxaban) and thrombin (FIIa; dabigatran, bilvalirudin, and argatroban). UFH, VKA, and LMWH have multiple targets within the coagulation cascade. Anticoagulants that are currently under development or undergoing clinical trials target factors from the TF pathway (TF-FVIIa complex) or the contact activation pathway (FIXa, FXIa, and FXIIa). Tenase complex: FVIIIa-FIXa complex. Prothrombinase complex: FVIIIa-FIXa-FXa complex [40].

3. FACTORS INFLUENCING PATIENT COMPLIANCE

Drug–Drug Interactions

Oral anticoagulants come with a lower burden for VTE patients, since no medical personnel or injections are required for their admission. With their rapid mode of action, especially the novel VTE drugs, DOACs are preferred over other currently used drugs. However, compared to parenteral anticoagulants, oral anticoagulants are often accompanied by the risk of undesired drug–drug interaction (DDI) [41]. DDIs are secondary to the specific effect of a therapeutic and can occur when two administered drugs share the same cell membrane transporter or metabolic pathway. Oral anticoagulants need to pass from the gastrointestinal system into the circulation, and, subsequently, they are metabolized by renal or hepatic clearance. Their transport to and from the circulation is mediated by the transporter glycoproteins, such as P-GP [42]. Drugs administered to treat atrial fibrillation may interfere with DOAC transport by P-GP, and this leads to an increase in the anticoagulant activity. For instance, dabigatran activity could increase by up to 70% in patients that are treated with dronedarone. For this reason, to treat atrial fibrillation, the drug amiodarone, a moderate P-GP competitor, is preferred to

dronedarone in patients using DOACs [43]. In cancer patients, imatinib and crizotinib, two tyrosine kinases, are contraindicated for DOAC patients, due to their strong inhibitory capacity of P-GP [87]. Enzalutamide, a prostate cancer hormonotherapy, promotes P-GP function, and this could reduce the concentration of the administered DOAC, resulting in an increased risk for recurrent VTE [88]. P450 cytochromes CYP2C9, CYP1A2, and CYP3A4 mediate the elimination of oral anticoagulants, and DOAC or VKA patients that receive P450-cytochromes-inhibiting drugs have an increased bleeding risk [44]. Drugs to treat atrial fibrillation and cancer are most often cited for their DDI with oral anticoagulants, but DDIs with statins and antibiotic, antidepressant, and antiviral drugs have also been described [44].

Certain intrinsic characteristics of individual patients may cause anticoagulants to have a different metabolism. It has been demonstrated that polymorphisms on transporters or P450 cytochromes can lead to unexpected variability in drug efficacy [45]. The same holds true for polymorphisms in the VKCOR1 gene, the target of VKAs, which can cause individuals to have a delayed response towards the drug. Patients with liver or kidney failure demonstrate a delay in the elimination of anticoagulants, thereby increasing the plasma concentration and the risk of bleeding [45, 46, 47].

4. INTRODUCING DOACS IN COMPLEX PATIENT POPULATIONS

In many clinical trials to investigate the effects of a certain drug, children are excluded due to their physical vulnerability [48]. For this specific patient population, the use of DOACs to prevent or cure (recurrent) VTE will most likely significantly improve the quality of care, since the drug is administered orally and it does not require intense monitoring. The EINSTEIN Junior study was the first study designed to test DOACs in pediatric VTE patients [49]. Within this study, the efficacy and the safety of rivaroxaban was compared to regular treatment, i.e., treatment with VKA, LMWH, or UFH. Within four years, more than 500 children were recruited, and patients treated with rivaroxaban demonstrated a similar recurrence risk of VTE and bleeding risk, compared to other anticoagulants. Currently, the EINSTEIN Junior study is the largest study to be carried out in children testing DOACs, and, although DOACs appear safe and effective in pediatric VTE patients, we must remain vigilant for their use in this vulnerable population

Heparins are the only anticoagulants that are authorized during pregnancy, since VKAs and DOACs pass the placental barrier. However, unlike for VKAs, the exact effects of DOACs on the developing fetus are unknown. In 2020, a registry of women who had been pregnant while receiving DOACs was published by Beyer-Westendorf et al. [50]. In that registry, from 2007 to 2020, 336 mothers were included that were exposed to DOACs during pregnancy. In total, 6% of the women displayed a non-normal fetus growth (95% confidence interval 4%–9%, comparable to the normal population). Despite these promising results, physicians remain reluctant to prescribe DOACs in pregnant women. In addition, DOACs are assumed to pass into breast milk, so, for this reason, the drugs are currently not prescribed in nursing mothers [51, 52].

The RAPS and TRAPS clinical studies were designed to evaluate DOACs in preventing VTE in triple-positive antiphospholipid syndrome (APS) patients [53, 54]. Although the first study provided promising results, making use of a biologic test as a clinical surrogate marker [55], the second study was prematurely stopped due to a major safety issue [56]. It appeared that the use of the anti-FXa DOAC rivaroxaban was associated with an increased risk of thrombotic events, compared to VKA. Based on these results, the use of DOACs is, currently, strongly discouraged in APS patients. However, APS is a complex disease, for which the pathophysiology is not completely understood, so a dedicated study investigating the putative mechanism by which DOACs increase VTE risk in APS patients is required [57]. However, the aforementioned study only tested rivaroxaban and no other DOAC and did not include single- or double-positive APS patients, while real-life data of non-triple-positive APS patients who remained on DOACs are reassuring [58]. These shortcomings argue for new studies on DOACs in triple-positive APS patients.

In 2013, Eikelboom at al. published a study comparing dabigatran to warfarin in patients with mechanical heart valves [59]. The study was stopped prematurely because, for unknown reasons, an excess of thrombotic events in the dabigatran group was observed (32% vs. 6% in the warfarin group). Interestingly, in a recently published study, rivaroxaban-treated patients with organic heart valve disease-associated atrial fibrillation showed an increase in cardiovascular events and death in DOAC patients, compared to patients under VKA treatment [60]. These data strongly imply that DOACs should be avoided in patients with mechanical or organic heart valves.

After a pulmonary embolism event, optimal follow-up comprises monitoring for long-term complications, such as chronic thromboembolic pulmonary hypertension (CTEPH) [61]. The efficacy and safety of DOACs to prevent recurrent VTE is challenged because of a higher incidence of CTEPH, compared to VKA-treated patients, possibly because of clinically relevant drug–drug interaction [61, 62]. Hence, updated guidelines recommend to prescribe VKA over DOACs in patients with CTEPH [63].

In atherosclerosis, the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) showed that combining regular aspirin treatment with rivaroxaban (2.5 mg twice daily) was beneficial for coronary, cerebrovascular, and peripheral end points in patients with and without diabetes mellitus [64]. The beneficial effect of aspirin and rivaroxaban has not been confirmed yet for VTE patients. Combination therapy using anticoagulants and anti-aggregants in DVT was assessed by a Cochrane meta-analysis [65]. Following the initial standard treatment with anticoagulants, there appeared to

be low-certainty evidence that antiplatelet agents, in addition to standard anticoagulation and other clinical practices (like stocking socks), reduce recurrent VTE, with no clear differences of adverse events such as major bleeding or recurrent VTE. For PE, no recent studies have been published on the subject of combination therapy. Fear of bleeding events should not be an obstacle to the production of reassuring data on the risk of bleeding associated with anticoagulant and anti-aggregant combination therapy [66]. However, dedicated studies are needed to explore the potential of combining drugs to prevent or cure VTE.

5. STRATEGIES TO IMPROVE ADHERENCE

A study by Eyob Alemayehu et al. [67] Clinical guidelines on atrial fibrillation management help optimize the use of oral anticoagulants. However, guideline non-adherence is common, particularly in the primary care setting. The primary aim of this systematic review was to identify effective strategies for improving adherence to guideline-directed thromboprophylaxis to patients with atrial fibrillation in the primary care setting. A search was conducted on 6 electronic databases (Medline, Embase, ScienceDirect, Scopus, the Cumulative Indexing of Nursing and Allied Health Literature, and Web of Science) supplemented by a Google advanced search. Studies aimed at improving oral thromboprophylaxis guideline adherence in patients with atrial fibrillation, in the primary care setting, were included in the study. A total of 33 studies were included in this review. Nine studies employed electronic decision support (EDS), of which 4 reported modest improvements in guideline adherence. Five of 6 studies that utilized local guidelines as quality improvement measures reported improvement in guideline adherence. All 5 studies that employed coordinated care and the use of specialist support and 4 of the 5 studies that involved pharmacist-led interventions reported improvements in guideline adherence. Interventions based mainly on feedback from audits were less effective. Multifaceted interventions, especially those incorporating coordinated care and specialist support, pharmacists, or local adaptations to and implementation of national and/or international guidelines appear to be more consistently effective in improving guideline adherence in the primary care setting than interventions based mainly on EDS and feedback from audits.

6. CONCLUSION

Anticoagulant therapy remains a cornerstone in the management of cardiovascular diseases, yet adherence challenges persist, impacting treatment efficacy and patient outcomes. Addressing barriers to compliance requires a comprehensive strategy, integrating patient education, healthcare provider engagement, and technological advancements to optimize anticoagulation management. Future research should focus on long-term adherence patterns with novel anticoagulants and the effectiveness of tailored interventions to enhance patient compliance.

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I would like to share my gratitude to my guide.

Conflict of Interest

No Conflict of Interest were found.

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