The Efficacy and Safety of Anticoagulants Therapy in Cardiovascular Disease Management in Modern Medicine

By

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Declaration

It is hereby declared that

1. The project submitted is my/our own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

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Ethics Statement

This study does not involve any human or animal trial

Abstract

As cardiovascular diseases (CVDs) remain a major global health concern, ongoing advancements in therapeutic approaches are essential. Anticoagulant therapy is one of these strategies that have become an essential component for managing CVDs, providing significant advantages in terms of lowering thrombotic events and enhancing patient outcomes. This abstract presents a summary of the safety and effectiveness of anticoagulant therapy in the management of modern cardiovascular disease, combining data from guidelines, clinical trials, and recent literature. Cardiovascular care is constantly as shown by the development of anticoagulant agents, which have improved efficacy, safety profiles, and convenience. This research sets out to determine factors influencing therapeutic choice-making, evaluate safety profiles, investigate the effect of anticoagulant agents on clinical practice guide lines, and evaluate the efficacy of different anticoagulant agents through an in-depth review.

Key Word: Cardiovascular Disease (CVds), Anticoagulant therapy, Thromboembolism, Direct Oral Anticoagulant, warfarin, Clinical guidelines, Evidence- based practice, Safety profile, Efficacy, Clinical Trial.

Dedication

I would like to dedicate this manuscript to my parents.

Acknowledgement

First and foremost, I would like to express my gratitude to Allah for all of his blessings, which have given me the perseverance and determination to complete this project. I would like to take this opportunity to thank my academic supervisor, Dr.Sabrina Sharmin(Assistant Professor at the School of Pharmacy at BRAC University) for her guidance and encouragement while writing this manuscript. Throughout my studies and project writing, she was a true source of support and motivation. Lastly, I want to express my gratitude to my family for constantly inspiring me to step beyond of my comfort zone. I could not have made it this far without my family's and loved ones' constant support and prayers.

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List of Acronyms

ACCP	American College of Chest Physicians
AF	Atrial Fibrillation
AI	Artificial Intelligence
ATIII	Antithrombin III
CHD	Coronary Heart Disease
CVD	Cardiovascular Disease
DOACs	Direct Oral Anticoagulants
DVT	Deep-vein Thrombosis
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
INR	International Normalized Ratio
LMWH	Low Molecular Weight Heparin
NSAIDs	Nonsteroidal Anti-inflammatory Agents
PE	Pulmonary Embolism
VTE	Venous Thromboembolism

Chapter 1

1.Introduction:

1.1Global Burden of Cardiovascular disease:

Cardiovascular disease is one of the most significant public health concerns worldwide. According to WHO, approximately 17.9 million deaths are occurring due to cardiovascular disease. CVds are consists of disorder of heart and blood vessel and involves in coronary heart attack, thromboembolism. A significant percentage of this affliction is associated to thromboembolic complication like ischemic stroke, pulmonary embolism, deep vein thrombosis and these are responsible to severe disability and death if it remains untreated (Benjamin et al., 2019). For example, atrial fibrillation exhibit risk of stroke and myocardial infraction which lead to ventricular thrombus formation and embolic incident (January et al.,2014; Ibanez et al.,2018). Despite the strides that have been achieved in addressing challenges confronting our health systems, much work is yet to be done to improve therapy strategies (American Heart Association, 2021).

1.2 Rationale of Anticoagulant Therapy:

Anticoagulants have increasingly been recognized as an integral management for CVDs for the complex nature of thromboembolic accidents (Kearon et al., 2016). Anticoagulant therapy is benefited for it's ability to inhibit clot formation by that reduces risk of stroke, venous thromboembolism, myocardial infraction. Superiority in terms of effectiveness, safety, convenience, and simplicity of administration of anticoagulants compared with conventional therapy has led to a favorable development of oral anticoagulants over time (Raskob et al., 2018).Anticoagulant therapy is involved in a crucial role in both the prophylaxis and treatment of such conditions. Prophylactically, it works by preventing clot formation in high risk patient like in case of atrial fibrillation, mechanical heart valves, and post major orthopedic surgery. Whereas, therapeutically, Anticoagulant lower mortality and complications by treating designated thromboembolic events including pulmonary embolism and deep vein thrombosis (Konstantinides et al.,2019).Clinical evidence assisted their usage in several population for example, a large registry review revealed that relevant and adequate anticoagulant can reduce the risk of ischaemic stroke by as much as 64 percent in atrial fibrillation (Hart et al., 2007). Expedited better patient outcomes, knowledge, and technology advances inspire new medical devices, products, and

procedures. The present study endeavors to analyze the safety and efficacy of anticoagulant medications for cardiovascular diseases based on modern medicine, considering the reasons indicated above.

1.3 Anticoagulant therapy in COVID-19:

The COVID-19 pandemic made the significance of anticoagulation gradually more evident. Observational data and autopsy results showed that, across hospitalized COVID-19 patients, VTE incidence rates in intensive care units might reach 27 percent despite regular prophylactic, including PE being the most frequent occurrence (Middeldorp et al., 2020). Between 1% to 6% of hospitalized patient experienced stroke , specially those with severe illness and increased D-dimer having a higher risk (Nannoni et al.,2020). When compared to prophylactic dosing , therapeutic dose heparin in moderately ill patients decreased the combined outcomes of VTE,arterial thromboembolism or death by 13 percent but the biggest benefit seen in reduction of PE and DVT rates according to meta –analyses of randomized controlled trials (Lawer et al., 2021;Sholzberg et al.,2021) . To balance clot prevention against bleeding risk, professional guidelines such as ASH, NIH, ISTH) now recommend therapeutic anticoagulation in non ICU patients with high thrombotic risk and standard prophylaxis in critically ill patients.

1.4 Evolution of Anticoagulant Drugs:

Traditionally, the cornerstone of long term anticoagulation was vitamin K antagonists such as Warfarin. VKAs are considered useful, although they have a limited therapeutic window, many drug-food interactions, and frequent INR monitoring. Practice has changed dramatically during past ten years due to the emergence of novel oral anticoagulants (NOACs), which also referred as direct oral anticoagulants like dabigatran, apixaban and rivaroxaban. These medications have better clinical outcomes and patient adherence than warfarin. In large population trials, they also showed decreased incidence of cerebral haemorrhage (Connolly et al., 2009; Patel et al., 2011; Granger et al.,2011). This research program assesses the role, comparative efficacy and changing strategies in anticoagulants in various forms of cardiovascular disease through systematic scoping review of the evidence base (literature, clinical trials, guidelines).

1.5 Rationale of the project:

Thromboembolic events like stroke, pulmonary embolism, deep vein thrombosis are vitally responsible for Cardiovascular morbidity and mortality (Virani., 2021). Anticoagulants is a crucial drug for both prevention and treatment (Weitz et al., 2016). However Warfarin has been effective it has also limitations like continuous INR checks, dietary restrictions and drug interactions. But innovation of Novel Oral Anticoagulants brought a new milestone which is also known as Direct Oral Anticoagulants. They offer predictable dosing, improved clinical outcomes, fewer interactions, better safety profiles. This project seeks to integrate clinical evidence and guideline recommendations to enhance the safe and effective use of anticoagulant therapy in cardiovascular disease.

1.6 Objective of the project:

This project aims to review and analyze evidence based practices in anticoagulant therapy for cardiovascular disease. This Project focuses on improving patient outcomes by optimized drug selection, personalized care and adherence strategies. It has particular goals, they are;

- It briefs current guidelines for anticoagulant usage in conditions such as atrial fibrillation, myocardial infraction, pulmonary embolism snd deep vein thrombosis.
- Defines and compare between traditional vitamin k antagonist and novel oral anticoagulants.
- Identify factors contributing to non-adherence to anticoagulant therapy and purpose evidence-based strategies to improve patient knowledge and promote consistent medication use.

Chapter 2

Methodology

The information was obtained from peer reviewed journals, research papers, articles available in databases such as PubMed, Frontiers, Springer, MDPI, ScienceDirect, Google Scholar and so forth. Significant keywords such as diabetes, metformin, glucose, hypoglycemia was used to search literatures. On the basis of the topic, relevant and useful articles were gathered, and further context was investigated. After deciding on a theme, an outline was prepared with appropriate headings and subheadings. Mendeley Desktop provided the bibliography and in-text citations. The entire essay was paraphrased, and the writing included citations.

Chapter 3

Mechanism of Anticoagulants:

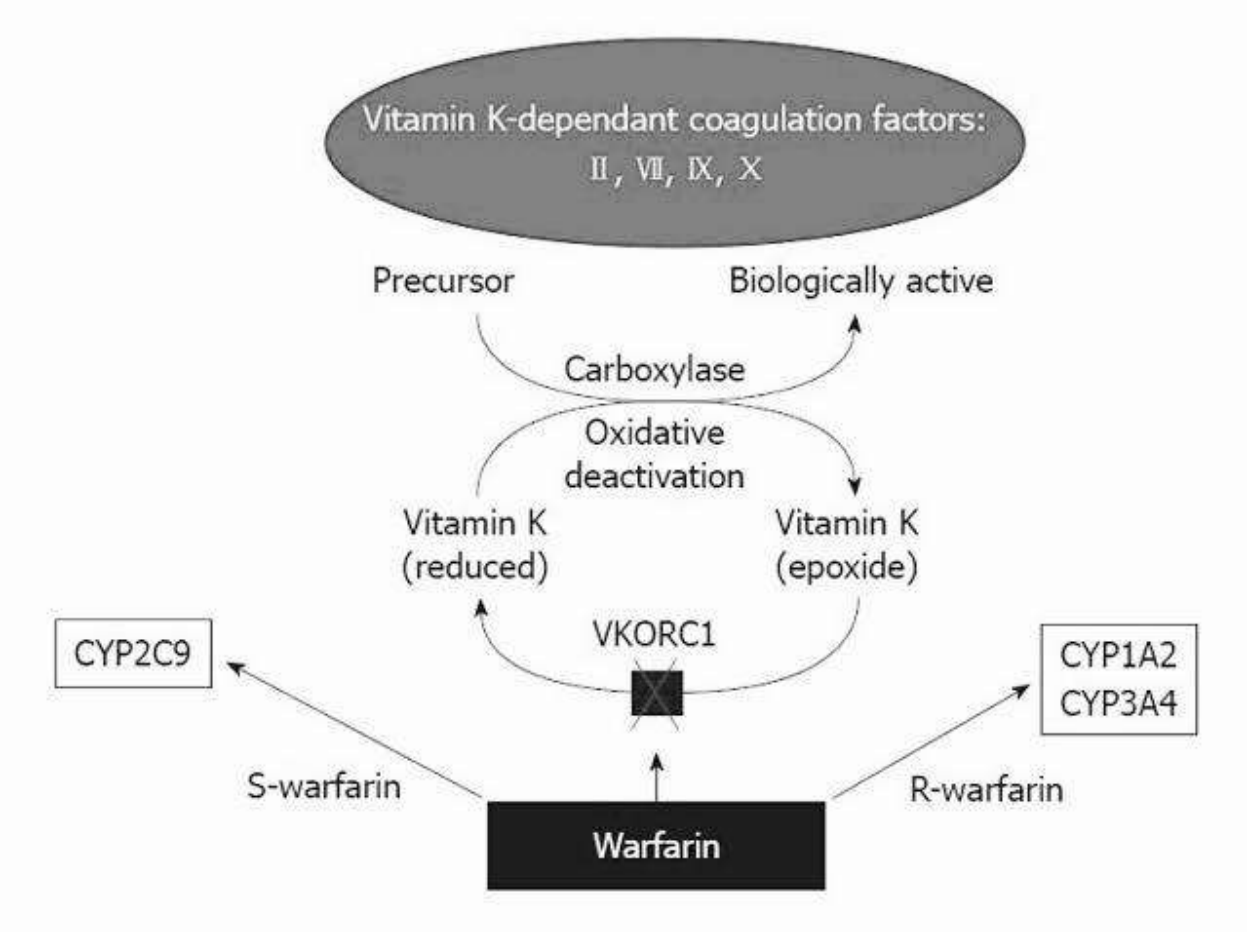
3.1 Anti-coagulant:

They act by blocking the coagulation process i.e., prevent the formation of blood clot. Their emphasis is on different parts of the pathway of coagulation, a cascade of enzrnatic reactions that leads to clot formation. For example, antithrombin III (ATIII), a naturally occurring inhibitor of thrombin and factor Xa) is further activated by heparin and its precursors, including low molecular weight heparin (LMWH). By binding to ATIII, heparin accelerates its inhibition of throbmin and factor Xa, two key enzymes associated with the final steps of the clotting process (Weitz, 1997). It thus finally inhibits fibrin formation by preventing the conversion of fibrinogen into fibrin (the insoluble protein that forms the network in cells of a blood clot).

Analogous to this mechanism, vitamin K antagonists like warfarin inhibit the liver´s production of vitamin K-dependent clotting factors (II, VII, IX, X). Vitamin K is needed inside the body in order for these clotting factors to be gamma-carboxylated and hence to be functional.

Warfarin prevent its accumulation by interfering with this process, which reduces synthesis of the functional clotting factors produced (Fasco et al.,1982).

Specific aspects of the coagulation cascade are the action site of direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, and edoxaban. The specific factor Xa inhibitors are rivaroxaban, apixaban, and edoxaban; dabigatran directly inhibits thrombin (factor IIa). The fact that DOACs inhibit these significant enzymes means that they act as anticoagulants and so don't allow the coagulation process to move forward (Chan & Weitz., 2019).



Mechanism of Anticoagulants (warfarin) 1

(Rubboli et al., 2011)

Chapter 4

Anticoagulant Treatment Efficay:

4.1 Clinical Trial of Anticoagulant in different CVDs:

4.1.1 RE-LY Trial (Atrial Fibrillation):

Methods and Results: In the RE-LY trial, safety and efficacy of warfarin versus dabigatran, a direct thrombin inhibitor, were studied in patients with atrial fibrillation.

• **Results:** Both 110 mg and 150 mg doses of dabigatran decreased the risk for stroke and systemic embolism compared with warfarin or were non-inferior to it and were associated with lower cerebral hemorrhage risk (Connolly et al., 2009).

4.1.2 EINSTEIN Trials (Deep Vein Thrombosis and Pulmonary Embolism):

• **Design:** The EINSTEIN studies compared rivaroxaban with conventional therapy for acute deep-vein thrombosis and pulmonary embolism (ie, enoxaparin followed by a vitamin K antagonist).

• **Results:** Safety for rivaroxaban was similar to standard therapy and more effective (Buller et al.,2010; Bauersachs et al.,2010).

Design of Studies: The EINSTEIN trials (Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism) investigated the safety and efficacy of rivaroxaban as compared with standard therapy (enoxaparin followed by a vitamin K antagonist) for the treatment of severe DVT and pulmonary embolism.

Results: Rivaroxaban was found to be as safe as standard therapy and not non-inferior to it

4.1.3 The Aristotole Trial (Atrial Fibrillation):

• **Study Design:** Atrial fibrillation (AF) patients in the ARISTOTLE trial were randomized to apixaban, a direct factor Xa inhibitor, or to warfarin.

• **Results**: Based on a comparison of trial medication with warfarin, apixaban was superior for the prevention of serious bleeding events, stroke, or systemic embolism (Granger et al., 2011).

4.2 Comparison of Efficacy of Anticoagulants:

4.2.1 Warfarin:

- Warfarin and treatment of venetron thromboembolism and atrial fibrillation. This procedure uses the medieval vitamin K antagonist.

- Even though warfarin is effective, it does require regular recalibration of the dose and monitoring of the INR, or international normalization ratio, to make sure it is within the ideal range.

- The findings suggest that warfarin reduces the risk of stroke and embolism by large margins in patients with atrial fibrillation and that it also effectively prevents the recurrence of thromboembolism.

4.2.2 Direct Oral Anticoagulant:

- In contrast to warfarin, DOACs including dabigatran, rivaroxaban, apixaban, and edoxaban have several advantages including fixed doses, predictable pharmacokinetics, and no need for routine monitoring.

- In head-to-head clinical trials, DOACs and warfarin perform equally well (or poorly) in preventing thromboembolism in varied clinical settings. For examples, the RE-LY trial (Connolly et al., 2009) found that dabigatran recipients developed no more, and perhaps fewer, strokes and systemic emboli than those who took warfarin for atrial fibrillation.

- Also in patients with atrial fibrillation, warfarin was shown to be better than warfaround and apixaban in the aristotle trials (Granger et al., 2011).

- Safety Different anticoagulants have been used as prevention for arterial and VTE.

Chapter 5

5.1 Concerns about the safety of anticoagulant:

5.1.1 Bleeding Risk:

The most significant side effect of anticoagulants is the risk of bleeding. This risk may involve minor injuries, such as nosebleeds or bruises, as well as catastrophic ones, such as intracerebral haemorrhaging or gastrointestinal bleeding.

The risk of bleeding and other factors that influence the risk of bleeding in this setting are patient age, renal function, type of anticoagulant, dosage, duration of therapy, and concomitant drug therapy.

5.1.2 Adverse Effect:

There are other side effects from anticoagulant medications including rash, nausea, allergic reactions, liver damage, and gastrointestinal symptoms, as well as bleeding.

Warfarin is an example of an anticoagulant with a narrow therapeutic window. Both drug-drug interactions and dietary vitamin K intake contribute to over or under-anticoagulation.

5.1.3 Monitoring and management:

Therapeutic adequacy and bleeding risk of VKAs are achieved at the price of regular monitoring of the INR and adjustment of VKA dose: whereas for DOACs the situation is more complex, and will depend on the drug (renal function in the case of DOACs).

Administration of specific reversal agents, such as vitamin K, prothrombin complex concentrate, blood product transfusion, and temporary suspension or dose reduction of anticoagulant therapy represent the approaches for the treatment of bleeding.

5.1.4 Patient Education and Counselling:

Patient education and counseling are crucial to help patients comprehend the risks and benefits of anticoagulant use, recognize the signs and symptoms of bleeding adhere to dosing recommendations and comply with monitoring.

5.2 How to Monitor and Address Safety Concerns:

5.2.1 Regular Monitoring:

When therapeutic warfarin is maintained within the target range using INR monitoring, clinicians can reduce the likelihood of both bleeding complications and thromboembolism.

5.2.2 Monitoring of the Renal Function:

- Monitor renal function to avoid medication absorption and bleeding complications due to renal exclusion of certain DOACs (i.e., dabigatran and rivaroxaban) in patients with impaired renal function (Douketis et al).

- Serum creatinine levels and estimated glomerular filtration rate (eGFR) are two renal function markers that should be assessed systematically to identify patients in whom different anticoagulant therapies, or dose adjustments, could be beneficial.

5.2.3 Dose Adjustment:

- In order to maximize the safety and effectiveness of such anticoagulant therapy, specific dosing adjustments are needed for patient-specific factors, such as age, weight, renal function, and concurrent use of drugs (Douketis et al., 2012).

- Elderly, hepatic or those at risk of haemorrhage may require dose adjustments.

5.2.4 Compliance with Standards:

- Groups such as the American College of Chest Physicians (ACCP) can issue evidence-based practice guidelines and introduce comprehensive programs for proper and efficient management of anticoagulant safety (Holbrook et al., 2012).

- Health care providers need current recommendations to help guide clinical judgment and optimize patient care.

Chapter 6

Role of Anticoagulants in Particular Cardiovascular Disease:

6.1 Anticoagulant in certain CVDs:

6.1.1 Atrial Fibrillation:

- Atrial fibrillation is a common type of arrhythmia associated with a higher risk of stroke, since it generates blood clots in the atria.

- In elements that can decrease the risk of thromboembolic events, such as stroke in patients with atrial fibrillation; specifically when oral anticoagulants are included.

- Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban, and edoxaban, are recommended for stroke prevention in patients with non-valvular atrial fibrillation. According to January et al. (2014), these drugs are no less safe or effective than warfarin.

- Choice of anticoagulant treatment for atrial fibrillation is based on a patient-specific profile including renal function, risk of bleeding, interactions with other drugs and patient preference.

6.1.2 Venous Thromboembolism:

- Both PE and deep-vein thrombosis (DVT), which are associated with significant morbidity and mortality, fall under venous thromboembolism.

- Anticoagulant therapy is necessary to manage episodes of acute VTE and to prevent recurrences.

- Because of their greatering effectiveness, safety, and ease-of-use compared with parenteral anticoagulant therapy followed by a vitamin K antagonist, all DOACs—apixaban, dabigatran, edoxaban, and rivaroxaban— are recommended as first-line treatments for acute VTE and for extended anticoagulation to prevent recurrence (Konstantinides et al., 2019).

6.1.3 CAD Corresponds To:

- Anticoagulant therapy can be used to treat ACS, CAD, and AF.
- People with ACS, the initial treatment of choice is DAPT treatment (aspirin and P2Y12 inhibitor) to prevent recurrent ischemic events. Some high-risk patients, such as those undergoing PCI, might benefit from adding anticoagulants (i.e., unfractionated heparin, low molecular weight heparin, or bivalirudin) (Ibanez et al., 2018).
- When choosing a specific anticoagulant for a patient with AF and known CAD, consideration should be given to the need for concomitant antiplatelet therapy for the prevention of both arterial thromboembolic disease and atherothrombotic events. Warfarin is not recommended in these patients given the favourable safety and efficacy profile of the DOACs (Hindricks et al., 2021)

6.2 Guidelines and Considerations for Conditions:

6.2.1 Atrial Fibrillation:

Rules:

- Full recommendations for the management of AF can be found in guidelines produced by the AHA, HRS, and the ACC (January et al., 2014).
- European Society of Cardiology (ESC) guidelines, for the diagnosis and treatment of atrial fibrillation have been published (Hindricks et al., 2021).

Ideas:

- Patients with atrial fibrillation and a CHA2DS2-VASc score of two or higher should take an oral anticoagulant to reduce the risk of stroke. Due to their favorable effective, safety and convenience profile, the vast majority of patients prefer DOACs to warfarin.

Chapter 7

Special population and consideration:

7.1 Special Population Baseline: The special population for anticoagulant therapy:

7.1.1 Elderly Patients:

- The elderly are especially prone to thromboembolic episodes and bleeding complications because of age-related co-morbid conditions, concomitant diseases, and multiple drug use.
- Younger patients with atrial fibrillation may derive a stroke-mitigating benefit from anticoagulation; For older individuals, studies suggest, but the challenge becomes deciding which anticoagulants to use and in what dosage to minimize the risk and maximize the benefit (Cuker et al., 2019).
- Renal function must be assessed since most DOACs are renally cleared. Nevertheless, older patients are more commonly treated with DOACs, partly due to their fixed dosing and predictable pharmacokinetics, and the absence of a requirement for monitoring (Cuker and others, 2019).

7.1.2 Pregnant Women:

- Anticoagulation therapy during pregnancy is fraught with possible danger to both the mother and fetus and should be approached with caution. The teratogenic effects of warfarin and other vitamin K antagonists render them usually contraindicated, especially during early pregnancy.
- Low molecular weight heparin (LMWH) is the anticoagulant of choice during pregnancy as it is not placenta penetrating with extensive evidence of safety for both mother and baby (Bates et al, 2018).
- If postpartum anticoagulation is still necessary, oral anticoagulants may be an option, but they need to be monitored closely, particularly in nursing mothers.

7.1.3 Renal Patients:

- Renal insufficiency affects the clearance of many anticoagulants especially DOACs which are renally eliminated to some extent or mostly.

- Dose adaptation is required in renal impairment on account of build-up and bleeding risk, with preference for warfarin as opposed to DOACs since it is not renally excreted. (Camm et al., 2012)

- Renal function should be monitored in all patients receiving DOACs, especially for older patients or those with variable renal function.

7.1.4 Hepatic impairment:

- Hepatic function: Anticoagulants that are metabolised by the liver could have their metabolism altered in hepatic insufficiency (e.g.warfarin and certain DOACs).

- DOACs should be used cautiously or not at all in patients with moderate to severe liver damage because liver disease can influence drug metabolism and increase the risk for bleeding. (Camm et al., 2012)

- Attention to the INR is important because hepatic dysfunction can affect warfarin metabolism and sensitivity, but stable patients with liver disease may be candidates for warfarin.

7.2 Dosage adjustment and Monitoring Specific Populations:

7.2.1 Elderly Patients:

- Due to aging-induced alterations of pharmacokinetics and pharmacodynamics, higher rates of renal impairment and bleeding risk, older patients often require modified anticoagulant doses.

- Elderly patients treated with direct oral anticoagulants (DOACs) such as apixaban and edoxaban may need dose adjustments, particularly if they have other risk factors including small body weight or use of other drugs that affect drug metabolism (Cuker and others, 2019).

- To prevent overdosing as well as drug accumulation that could lead to bleeding, assessment of renal function is recommended in older patients treated with DOACs (Cuker and others, 2019).

7.2.2 Patients with Renal Impairment:

- Since anticoagulants such as dabigatran and rivaroxaban are a drug of the kidneys, patients with impaired function of the kidneys need to have dosages reduced to prevent

  high levels of the drugs from developing in their blood and to minimize issues related to bleeding.

- Accordingly, dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) and the dose should be reduced for patients with mild to moderate renal impairment (creatinine clearance 30–50 mL/min) (Camm and others, 2012).

- Since changes in drug clearance might be more pronounced in elderly patients with age-related decreases in renal function, monitoring of renal function should be undertaken both at baseline and periodically during treatment.

7.2.3 Hepatic Impairment Patients with hepatic impairment:

Individuals with moderate or severe hepatic impairment are classically not included in studies or included with a warning sign and a recommendation that DOACs be used with caution or not used at all, because of the potential risk of increased risk of bleeding. Warfarin may be used with caution, and liver dysfunction may alter the sensitivity and metabolism of warfarin; therefore, INR should be carefully monitored. (Camm et al., 2012)

Patients receiving long term therapy with anticoagulant and high risk of developing progressive liver disease and/or receiving concomitant hepatotoxic drugs should be monitored for liver function.

7.2.4 Concurrent medication use:

Concomitant medications that alter metabolic or absorption pathways of CYP3A4 or P-glycoprotein may modulate the safety and efficacy of DOACs.

For example, due to higher drug exposure, patients receiving strong CYP3A4 inhibitors such as ritonavir or ketoconazole may require lower doses of rivaroxaban or apixaban. (Kearon et al., 2016)

If there are potentially clinically important interactions, alternative therapies should be considered, with close observation of potential drug interactions.

Chapter 8

Cost effectiveness and Healthcare utilization:

8.1 Incremental cost effectiveness of Anticoagulants against Warfarin:

8.1.1 Direct Oral Anticoagulants vs Warfarin:

- In conditions like atrial fibrillation and venous thromboembolism, several cost-effectiveness studies have been conducted on DOACs (i.e., apixaban, rivaroxaban, and dabigatran) in comparison to the warfarin.

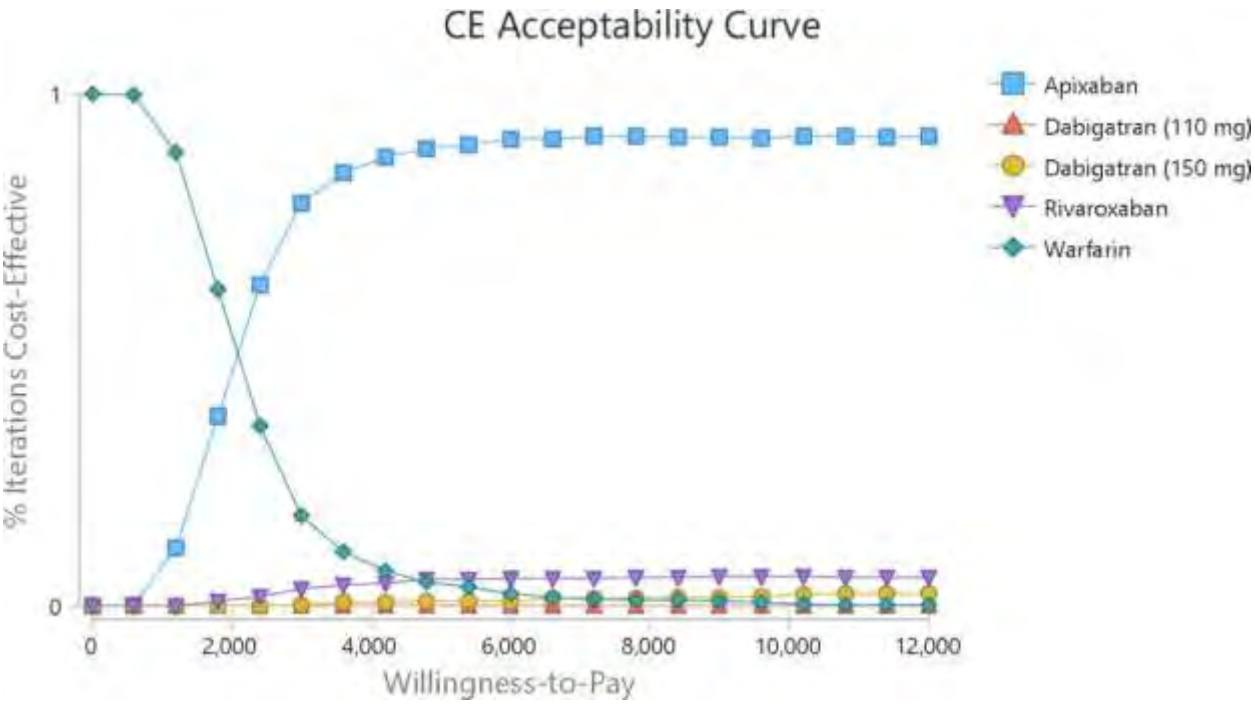
- DOACs avoid routine INR monitoring, carry a lower risk of bleeding complications, and are associated with fewer incidents of thromboembolic events and are often considered cost-effective in spite of their higher up-front costs relative to warfarin (Kamel et al., 2017; Amin et al., 2014).

- For example, despite higher costs, apixaban was shown to be cost-effective in patients with atrial fibrillation owing to the very good safety profile, particularly in reducing bleeding events, leading to a reduction of long term health care costs (Amin et al., 2014).

8.1.2 Comparative CE of the DOACs:

- Within the DOAC class, cost-effectiveness differs by the specific pharmacological properties. Some studies indicate that apixaban, especially for older patients, would offer the greatest value due to its combination of safety and efficacy. (Verma et al., 2018)

- Comparison studies suggest that rivaroxaban and apixaban, in particular, could provide health care savings when total health care costs are considered, including those associated with major bleeding and recurrent thromboembolism, relative to dabigatran (Verma et al., 2018).



Cost Effectiveness in DOACs 1

(Rezaei et al., 2024)

8.2 HCUs WHO RECEIVE ANTICOAGULATION THERAPY:

8.2.1 - Hospitalization due to an adverse event:

- Thromboembolic events, bleeding complications and the need for regular observations are the reasons why anticoagulant therapy appears to be associated often with a rising in the

number of hospitalisations especially if combined with more traditional drugs such as warfarin. Limited therapeutic margin of warfarin and unpredictability of its pharmacokinetics make the patient prone to major and minor bleedings, which frequently warrants... the need for emergency assistance (Lip et al., 2016).

- Due to their predictable pharmacokinetics and lower need for monitoring, DOACs, such as rivaroxaban and apixaban, have been associated with fewer hospitalization for bleeding, including cerebral hemorrhage (Sharma et al., 2020).

8.2.2 Less Consumption of Health Care Resources with DOACs:

Research demonstrates that patients on DOACs have fewer lab tests, clinic visits and dose-adjusting medical interventions leading to a cost savings and adherence increase (Lip et al., 2016; Sharma et al., 2020).

8.2.3 Visit to Emergency Room and Readmission:

- Warfarin users—especially older adults who are at higher risk for under- and overanticoagulation—experienced higher rates of ED visits due to adverse drug events compared with DOAC participants. For example, research has shown that apixaban and edoxaban substantially reduce ED visits and readmissions for major bleeding as alternatives to warfarin (Chung et al., 2019).

- Finally, as per studies too DOAC may decrease the 30-day readmission rates in A-fibburdened patients and venous thromboembolism as it decreases the risk of bleeding and therapy related issues (Chung et al., 2019).

8.2.4 Overall economic effect to the healthcare system:

• DOACs are pricier, but they usually result in lower total health care spending because they can be administered with fewer hospital days and monitoring charges. DOACs have the potential to reduce healthcare utilization costs related to anticoagulation treatment by up to 30% according to one systematic review. This was primarily driven by a lower number of ER visits, hospital admissions and outpatient monitoring requirements (Kamel et al., 2017).

Chapter 9

Emerging trends and Future directions:

We believe that these diagnostic techniques should be used for the management of both endemic and epidemic outbreaks of the CCHF.

9.1 Recent Development of Anticoagulant therapy:

9.1.1 development of a new oral direct anticoagulant:

Direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, and apixaban, have revolutionized anticoagulant therapy within the past decade, due to fixed-dose, pharmacokinetic predictability, and rare monitoring requirements. In acutely ill patients, newer DOACs such as betrixaban are being used to reduce risks of venous thromboembolism (VTE) (Connolly et al., 2018).

After the DOACs, a parenteral often prolonged-infusion regimen (most commonly once daily) has been traditionally used; the first DOAC to be approved for this indication was betrixaban (a factor Xa inhibitor). It increases patient safety and improves their compliance due to minor renal elimination and lower risk to induce drug-drug interactions compared with prior agents. (Weitz et al.,2020)

9.1.2 Factor XI inhibitors:

Promising results to reduce clot formation and low bleeding risk is seen in factor XI inhibitors in research. Novel agents such as osocimab and asundexian that target factor XI in the coagulation cascade but with reduced roles in hemostasis offer the potential for effective anticoagulation with minimal risk of serious bleeding. (Nimjee et al.,2021)

Trials such as the AXIOMATIC-TKR study demonstrate a substantial reduction in bleeding versus commonly used anticoagulants – evidence suggesting that inhibitors of Factor XI may be the key

to the prevention of VTE post-surgery and stroke in patients with atrial fibrillation. (Nimjee et al.,2021)

9.1.3 When to Bypass and Consideration of Bivalent Agents in Special Populations:

Patients with HIT might derive a benefit from the new bivalent anticoagulants such as bivalirudin, which inhibits the two thrombin activity sites. Patients at risk for HIT are better off thanks to this class of drugs, which is powerfully antithrombotic in its own right and has no dependence on heparin (Warkentin and others, 2020).

• Moreover, patients receiving DOACs can respond to bleeding events by not taking drugs such as andexanet alfa (a reversal drug for Factor Xa inhibitors), thus offering an important benefit in terms of safety in the emergency setting (Levy et al., 2018).

9.1.4 RNA therapies and gene silencing techniques:

- Fitusiran is an antithrombin-generating drug which has shown promising results in maintaining hemostasis, and is one of the clotting modulating anticoagulants that are developed by gene therapy and RNA interference (Pasi et al., 2020).

- These treatments are a further move down the path to precision anticoagulation with individualized anticoagulant approaches that may be tailored to genetic and disease-specific features (Pasi et al., 2020).

9.2 Anticoagulant therapy in cardiovascular disease: current research and future developments:

9.2.1 Inhibition of factor XI and factor XII:

Unlike traditional anticoagulants, inhibition of Factor XI and Factor XII might have potential in reducing bleeding while also mitigating thrombotic risk, and for this reason these factors are currently under study as potential targets for therapy. Early phase clinical studies have shown certain promising results for molecules targeting Factor XI, e.g., milvexian and asundexian, in preventing VTE and reducing the risk of stroke in AF. (Granger et al.,2022; Weitz et al., 2022)

In the AXIOMATIC-SSP phase 2 study, factor XI inhibition could reduce ischemic events without significantly increasing the risk for bleeding, suggesting its future use for the treatment of thrombosis with a better benefit/risk showing. (Granger et al., 2022)

9.2.2 RNA- based therapeutics and Gene editing:

Through selective reduction of coagulation proteins synthesis, these gene-silencing and RNA-based strategies have helped to further optimize anticoagulation. For example, fitusiran is a siRNA therapy in development for hemophiliacs which targets antithrombin expression and may offer controlled anticoagulation through closely regulated gene knockdown. (Pasi et al., 2020)

CRISPR-Cas9 gene editing is under investigation for diseases with genetic predisposition for clotting complications as well. As these approaches are still early in clinical development, they hold promise as personalized and persistent anticoagulation therapy. (Xu et al., 2021)

9.2.3 Customization of Anticoagulant Dosing and Precision Medicine:

• Pharmacogenomics is one of the advances that allow more personalized anticoagulant therapy. For these reasons, to improve dosage and minimize adverse effects, genetic testing is performed for polymorphisms in warfarin-metabolizing genes, for example the CYP2C9 and VKORC1 polymorphisms (Becerra et al., 2021).

• I think DOACs is something where personalized medicine is being brought in. Machine learning–based algorithms are currently under development to predict bleeding and thrombotic risks in a patient to personalize the choice and dose of anticoagulation based on a patient's clinical, and genetic profiles (Krauss et al., 2020).

9.2.4 DOACS: Reversible And Safer:

Reversible DOACs are under development for rapid anti-coagulation therapy, as is one molecule, ciraparantag, which is currently under clinical testing for emergency scenarios requiring immediate reversal (Ansell et al., 2019).

Novel DOACs with a more favorable side effect profile such that vasculopathy and end organ bleeding are minimized are also being studied to maintain anticoagulant potency. This may result

in increased use of anticoagulants in patients being currently contraindicated for such treatment (elderly individuals, heavily impaired renal function) (Ansell et al., 2019).

9.2.5 Artificial Intelligence and Machine Learning in Anticoagulation Management:

• Patient-specific risk prediction and treatment decision-making are aided by the use of artificial intelligence (AI) techniques to improve anticoagulation treatment. The creation of machine learning algorithms to assess risk factors including renal function, comorbidities, and concomitant medication to recommend best AC dosing and monitoring strategy is ongoing (Krauss et al., 2020).

• By adapting anticoagulant therapy to real-time health data, the devices can enhance patient safety and reduce side effects (Krauss et al., 2020).

Chapter 10

Adherence and education of the Patients:

10.1 The Role of the Patient's Knowledge About and Understanding of Anticoagulants:

Patient education is essential to ensure that anticoagulant is appropriate. Education intervention programs may help to reduce adverse events due to poor adherence among the patient population and could play a role in increasing clinical outcomes, since patient knowledge of the importance of maintaining dosage compliance and food-drug interactions were shown to contribute to low adherence (Lip et al.,2022).

10.1.1 Understanding How Anticoagulants Work and What the Dangers Are

• Dietary limitations, the need for frequent INR (International Normalized Ratio) monitoring, and potential for drug interactions are all burdensome for patients on vitamin K antagonists (VKAs, e.g., warfarin). Lack of care can result in excessive bleeding or thrombotic complications (Holbrook et al.,2019).

• DOACs, including apaxaban and rivaroxabarn, require less monitoring, but patients still are required to be instructed on medication interactions, adherence, and renal function monitoring (Dai et al., 2021).

Educational Interventions:

• It has been shown that patient-focussed education interventions and personalized counseling improve adherence (Pereira et al., 2021).

• Studies have shown that pharmacist-led lectures, brochures, and multimedia programs improve patient understanding and reduce errors in medications (Pereira et al.,2021).

10.1.2 Factors influencing the anticoagulant treatment adherence:

Adherence to oral anticoagulation Oral anticoagulant activity depends upon drug adherence, and adher-ence can be influenced by several factors:

Complexity of treatment plan:

Compliance with medication is cumbersome in warfarin as compared to in DOACs because of the frequent INR monitoring and dietary adjustment (Kaatz et al., 2020).

DOACs are more adherent than warfarin due to their fixed dose and low interaction level compared with warfarin (Wachter et al., 2021).

Adverse effects and risks of bleeding:

• One of the commonest reasons for non-adherence, especially among the elderly, is the fear of bleeding. Studies have suggested that patients who understand better how to manage their symptoms and risk of bleeding are more likely to adhere to their treatment (Kassalainen et al., 2020).

The patient experience and belief:

• Misunderstandings of the role of long-term care could lead some to cease anticoagulants prematurely (Lip et al 2020).

• If patients think that the advantages of using anticoagulants are higher than the adverse effects, they will tend to be adherent to anticoagulants (Pereira et al., 2021).

10.1.3 Interventions to Enhance Adherence:

There are many ways to increase success in the clinical trial and anticoagulant adherence:

Patient centered counselling and shared decision making patients.

Patients are more adherent when they participate actively in their management. When decisions are shared, therapeutic adherence and satisfaction increase dramatically, studies show. (Lip et al.,2020)

Use of digital health tool:

Adherence was found to improve with electronic reminders and smartphone applications. Patients who used medication-reminding smart phone apps were significantly more adherent (Wachter et al). (2021).

Pharmacist-Led interventions:

Pharmacist-led anticoagulation clinics have demonstrated potential in enhancing patient education, monitoring treatment and reducing side effects. (Pereira et al., 2021)

10.1.4 Clinical outcomes related with Better Adherence:

The better adherence of treatment with anticoagulants also was associated with a lower risk of stroke, systemic embolism, and major bleeding events:

Stroke prevention in Atrial Fibrillation:

DOAC adherence, as compared to nonadherence, was associated with a 33% lower risk of stroke in AF patients. (Dai et al.,2021)

Recurrence of Venous Thromboembolism:

The resistance to anticoagulation may increase the risk of recurrence of VTE up to 50% during the first year of treatment. (Kaatz et al.,2020)

Lower Hospitalization Rates:

One study found that hospitalizations related to anticoagulants were 20% lower among individuals who received structured education and adherence support. (Holbrook et al., 2019)

10.2 Barriers to adherence of Anticoagulants therapy for CVDs:

A patient's, medication's, healthcare system's and socioeconomic factors influence adherence to anticoagulation treatment.

10.2.1 Patient related barriers:

Low Health Literacy and Knowledge:

Many have a good understanding of the importance of anticoagulant medication, how it works to keep clots from forming and the risks of falling off the regimen. (Kaatz et al.,2020)

Inadequate patient knowledge leads to misuse of medication and misinterpretation of dose schedules. (Holbrook et al.,2019)

Memory loss and cognitive decline:

Older people in particular, who are frequently prescribed anticoagulants, could forget to take medication and thus the effectiveness of their treatment is reduced. (Kassalainen wt al.,2020)

Fear of Side effects: Adding to a reluctance to adhere, patients experience apprehension about drug interactions, food restrictions, and lifestyle adjustments. (Lip et al.,2022)

10.2.2 Barriers in relation with therapy:

Regimen complexity:

In contrast DOACs have fixed dosage regimens, adherence to which is difficult with warfarin because of the need for regular monitoring of the INR and dietary restrictions. (Dai et al., 2021)

Adverse drug reaction and drug interaction: The ingested mandarins do not mix well with medicine, and people are more prone to have adverse reactions or drug interactions after taken with them.

Many commonly used drugs, including antibiotics and antiplatelet and nonsteroidal anti-inflammatory agents (NSAIDs), influence warfarin by fluctuating therapeutic range and patient dissatisfaction. (Holbrook et al.,2019)

10.2.3 Barrier related to health system:

Restriction towards routine monitoring:

INR monitoring and referral to specialists may be very difficult for patients living in rural or impoverished areas and this could lead to discontinuation of treatment. (Kaatz et al.,2020)

Poor communication from a health care professional:

Variable patient counselling by health care providers leads to confusion regarding dosing, monitoring, and dietary restrictions thus further compromising adherence. (Pereira et al.,2021)

10.2.4 Socioeconomic barrier:

Financial problems and the cost of the drug:

• In patients with no or suboptimal insurance, the high cost of DOACs represents a barrier, which may result in drug restriction or discontinuation (Lip et al.,2022).

Cultural challenges: Some patients may experience difficulties in adhering to their anticoagulant treatment as a result of language barriers and concerns about drug safety (Watcher et al.,2021).

Chapter 11

Conclusion:

Anticoagulant drugs are indispensable for the treatment of cardiovascular diseases, including atrial fibrillation (AF), pulmonary embolism (PE), coronary heart disease (CHD), and deep vein thrombosis (DVT). In high-risk populations anticoagulants have been proven by multiple clinical trials to reduce mortality and thromboembolic events. It has been shown that DOACs and the vitamin K antagonist warfarin effectively reduce the risk of stroke and systemic embolism in people with atrial fibrillation (AF). Warfarin has less of the risk of cerebral hemorrhage compared to DOACs (dabigatran, apixaban, or rivaroxaban), but has been proven to be equally effective. Incidence rates of VTE for anticoagulated patients are much lower, and those who are persistently at risk clearly have continuing benefit from chronic anticoagulation. Anticoagulants are used in acute coronary syndrome to reduce the risk of blood clotting and future cardiovascular events. Some of the most dangerous hemorrhages, large and inside the brain or skull, are made more likely by anticoagulant use despite their efficacy. DOACs tend to have better safety records and fewer major bleeding problems than warfarin. Older patients, those with a history of gastrointestinal bleeding or renal dysfunction, would need monitoring. The presence of reversal agents (idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors), as well as strategies such as dosage adjustments and regular international normalized ratio (INR) control (in patients receiving warfarin), represent a progress with regards to anticoagulant safety. Anticoagulation therapy, however, remains an indispensable treatment in CVD in general, as it weighs the risks of bleeding against the benefits of preventing clots and stroke. Upcoming studies such as trials with newer anticoagulants and individualised therapies will help to obtain more benefit and less harm.

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