Rivaroxaban and Dabigatran: prospects for use in the management of heart failure

Kuat Sultan¹, Kumar Akku², Yerzhanova Dana³, Abdalimov Bektsultan⁴, Bolysbek Dana⁵

¹ Master of the first year of study in the specialty «Molecular Biology and Genetics»; Istinye University; Republic of Turkey
² School of Medicine, Faculty of General practitioner, the 7th course; NJSC «Astana Medical University»; Republic of Kazakhstan
³ School of Medicine, Faculty of General practitioner, the 7th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁴ School of Medicine, Faculty of General practitioner, the 7th course; NJSC «Astana Medical University»; Republic of Kazakhstan
⁵ School of Medicine, Faculty of General practitioner, the 7th course; NJSC «Astana Medical University»; Republic of Kazakhstan

Abstract.
Scientific articles examine the effectiveness and pharmacokinetics of two oral anticoagulants, dabigatran and rivaroxaban, in the context of treating atrial fibrillation and chronic heart failure. Dabigatran, as a direct thrombin inhibitor, influences the thrombin zone and fibrinogen, preventing fibrin formation. Rivaroxaban, as a selective factor Xa inhibitor, blocks factor X activation. Both medications demonstrate high bioavailability and plasma protein binding. Studies on the efficacy of rivaroxaban in atherosclerosis and low-dose rivaroxaban in chronic heart failure did not reveal statistically significant reductions in cardiovascular risk. The findings emphasize the importance of further research and an individualized approach to selecting anticoagulants for optimal management of patients with diverse cardiovascular conditions.

Keywords:
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Introduction:

Heart failure (HF) remains a prevailing cardiovascular condition, questioning the effectiveness and optimality of current therapeutic strategies. Characterized by impaired cardiac function in maintaining normal blood flow, HF not only significantly deteriorates patients’ quality of life but also contributes to high morbidity and mortality worldwide. With a continual rise in cases and progression of the pathology across diverse age and gender groups, the quest for novel and effective treatment modalities becomes paramount.

Intensive research in pharmacotherapy has led to the development of new drug classes, such as direct oral anticoagulants (DOACs), representatives of which, like dabigatran and rivaroxaban, promise to redefine approaches to managing HF. Despite the widespread application of these medications, questions regarding their optimal use and efficacy in HF persist, providing room for further investigation and clarification of DOACs’ role in enhancing the prognosis of patients with this serious condition.

Recent studies have provided some insights into the efficacy and potential of DOACs, particularly dabigatran and rivaroxaban, in the context of HF. However, despite the presumed advantages of these drugs, there is currently no unified understanding of their role in managing cardiovascular complications in patients with this condition.

This article aims to systematically discuss recent research concerning the application of dabigatran and rivaroxaban in patients with HF. Emphasis is placed on new perspectives provided by data on the impact of these medications on clinical outcomes, including the risk of cardiovascular complications, patients’ quality of life, and overall survival.

This article underscores the significance of new data, highlights current research directions in HF pharmacotherapy using DOACs, and evaluates their potential for optimizing treatment and improving outcomes for patients with this condition. Illuminating new perspectives and possibilities for applying DOACs in HF represents a crucial step toward a more effective approach to managing this severe and prevalent cardiac condition.
Materials and Methods:

To conduct a literature review and systematize the obtained data, a search was conducted for scientific articles, reviews, and meta-analyses in medical databases such as PubMed, MEDLINE, and other relevant sources. The included studies encompassed the period from 2010 to 2023 and were restricted by the language of scientific publication (English). Keywords and phrases such as "anticoagulants," "heart failure," "atrial fibrillation," "dabigatran," "rivaroxaban," were utilized for the search and selection of pertinent studies.

Results:

1. Dabigatran

Mechanism of Action: Dabigatran, a direct thrombin inhibitor, exerts its effect on the factor II coagulation cascade. The molecule mimics the structure of a part of fibrinogen, influencing the interaction zone between thrombin and fibrinogen, thereby blocking the conversion into fibrin. Its chemical structure contains a benzyl-imidazole nucleus attached to an amido-phenylalanine moiety, perceived as a false arginine. The carboxylic group in the molecule enhances the drug's hydrophilic properties, allowing dabigatran to inhibit the pivotal role of thrombin in hemostasis [1-2].

Pharmacokinetics: Dabigatran is presented as a prodrug - dabigatran etexilate, which is activated in peripheral blood. Its maximum concentration (Cmax) is 146 ng/mL with a dosage of 150 mg twice daily, reaching peak time (Tmax) within 0.5 to 1 hour. The volume of distribution is 60-70 L, half-life is 12-24 hours, and its oral bioavailability is 7%. The primary excretion route is through urine (80%) and feces (20%), where it does not undergo metabolism but binds to glucuronic acid.

Indications and Contraindications: Dabigatran is approved for thrombosis prophylaxis in surgeries such as hip or knee replacement. However, there are limitations in its use among patients with severe renal impairment. It has also been used for treating deep vein thrombosis and pulmonary embolism. Particular attention is required for patients with moderate renal impairment, elderly (>75 years old), or concurrent use of amiodarone.
Special Use Cases: In patients with severe renal impairment, dose reduction is recommended. Additionally, dabigatran may interact with other medications, necessitating dosage adjustments. If discontinuation before surgery is necessary, stopping the intake 24 hours before the procedure is recommended. There is no specific antidote for dabigatran, and in cases of overdose or bleeding, supportive measures and administering coagulant reversals are recommended.

Clinicians face various factors when choosing anticoagulants for patients with atrial fibrillation (AF) and heart failure (HF). The decision relies on a multi-level assessment, considering diverse clinical factors.

One key aspect is assessing the risk of thromboembolic complications, such as stroke. Scoring systems like CHA2DS2-VASc are used to evaluate individual risk and determine the need for anticoagulation therapy.

In the presence of HF, considering the state of cardiac function is crucial. For instance, patients with reduced ejection fraction (LVEF) may have specific anticoagulation management needs. Data from the GLORIA-AF study highlight a significant proportion of patients with HF and low LVEF, which might impact anticoagulant choice.

Another factor is the risk of bleeding, evaluated using the HAS-BLED scale. This factor is also taken into account when deciding on anticoagulant prescription.

Assessing the combination of all these factors, including individual patient characteristics, medical history, and comorbidities, helps clinicians select an optimal anticoagulation strategy. Moreover, considering each anticoagulant's specificities, such as efficacy, safety profile, and interaction with other medications, is crucial.

In the context of GLORIA-AF study results, dabigatran represents a significant option for managing anticoagulation in patients with AF and concomitant HF, especially those with indications or specific attention to cardiac function.

Dabigatran, one of the representatives of the new generation of oral anticoagulants, underwent thorough examination in the GLORIA-AF phase II study. This study involved the analysis of 15,308 patients with atrial fibrillation, among whom 3679 had diagnosed heart failure,
providing valuable information about this subgroup's characteristics.

The study results highlighted several key points. Firstly, patients with AF and HF receiving dabigatran showed comparable stroke incidence rates compared to those without heart failure. However, high rates of overall and vascular mortality indicate a significant impact of this medication on the survival of patients with the combination of AF and HF.

An important point is also the high percentage of patients with HF who had low ejection fraction, which emphasises the importance of dabigatran in the management of this category of patients. Analysing the use of dabigatran in the context of other antiarrhythmic and antithrombotic drugs completes the picture of its efficacy and safety.

These results presented in the GLORIA-AF study have important implications for clinicians deciding on the choice of anticoagulation strategy in patients with FP and concomitant HF. They provide new aspects in the field of individualised treatment, focusing on reducing the risk of stroke and improving survival in this population.

The passage discusses a case of a patient on therapeutic anticoagulation experiencing a thromboembolic event despite the use of dabigatran, a direct oral anticoagulant (DOAC). It highlights the challenges in managing such cases and explores potential reasons for the failure of adequate anticoagulation. The primary issue here is the occurrence of a transient ischemic attack (TIA) despite seemingly appropriate dabigatran dosing, prompting investigations into the reasons for this therapeutic failure.

The relevance of this text lies in its exploration of factors contributing to suboptimal anticoagulation despite using DOACs like dabigatran. It emphasises the need to consider various factors when assessing anticoagulation 'failure,' including drug levels, patient compliance, drug interactions, absorption issues post-surgery, and genetic variations affecting drug metabolism.

Moreover, it delves into the complex absorption mechanisms and metabolic pathways of dabigatran, citing the importance of drug storage, absorption alterations post-bariatric surgery, and the impact of P-glycoprotein (P-gp)
efflux pumps on drug bioavailability. It also highlights a specific genetic variant associated with impaired metabolism of dabigatran, potentially leading to suboptimal drug levels.

The discussion extends to the differential diagnosis of thromboembolic events despite adequate anticoagulation, emphasizing conditions like myeloproliferative disorders, anti-phospholipid syndrome, and other less common procoagulant states that could contribute to such occurrences.

Overall, the text underscores the complexities involved in managing patients on DOACs, particularly dabigatran, and the importance of investigating various factors contributing to suboptimal therapeutic outcomes. It remains pertinent in addressing challenges in anticoagulation management, especially in cases where thromboembolic events occur despite seemingly adequate therapy.

The study was designed to assess the cost-effectiveness of two drugs, Dabigatran and Warfarin, in preventing stroke in patients with nonvalvular atrial fibrillation (NAF). Using a Markov model, researchers compared the two treatment approaches - adjusted-dose Warfarin and taking Dabigatran at a dosage of 150 mg twice daily - in patients older than 65 years of age with NAFP and Medicare insurance.

The results indicate a benefit of Dabigatran over Warfarin: increased quality-adjusted life expectancy (QALY) and reduced risk of stroke. However, the cost of Dabigatran for patients older than 65 years without insurance may be significant and create a financial burden, making it less cost-effective than Warfarin.

The evaluation also showed that the economic impact of Dabigatran is highly dependent on the cost of the drug, the economic valuation of the time a patient spends on therapy, and the cost of treating complications such as intracranial haemorrhage.

The gist of the study is that Dabigatran is more effective in preventing strokes in patients with NAF compared to Warfarin. However, its cost-effectiveness may vary widely depending on insurance coverage and the financial burden on patients. The cost of the drug and its impact on financial burden play a key role in determining the cost-effectiveness
This study provides important data for decision-making about the optimal treatment choice in NAFP, considering the financial aspects for both patients and the health care system.

2. Rivaroxaban

Mechanism of Action: Rivaroxaban is a selective direct factor Xa inhibitor for oral administration. Its effect on the coagulation cascade is through inhibition of factor X activation and factor Xa formation. This process plays a key role in coagulation through both intrinsic and extrinsic pathways. Importantly, rivaroxaban has a dose-dependent effect on prothrombin time and shows a high correlation with plasma concentration using the Neoplastin kit. It should be noted that assay results may vary when other reagents are used. In addition, rivaroxaban causes a dose-dependent increase in partial thromboplastin activation time and Heptest results. However, these parameters are not recommended for the evaluation of the pharmacodynamic effects of the drug. This indicates the need for more accurate measurement methods to evaluate the effects of rivaroxaban on the blood coagulation system.

Pharmacokinetics: When taken orally rivaroxaban is rapidly absorbed, its bioavailability is high (80-100%) and does not depend on food intake. It has moderate variability of pharmacokinetics (coefficient of variability 30-40%). It is bound to plasma proteins, excreted mainly in the form of metabolites (2/3 of the dose), partly by kidneys and through intestine. Participates in metabolism by CYP3A4, CYP2J2 isoenzymes. Systemic clearance is about 10 l/h, half-life 5-13 h. In elderly patients and in renal dysfunction plasma concentrations are higher, which may enhance pharmacological effect.

Indications and Contraindications: Rivaroxaban is used for prophylaxis of thrombosis after joint surgery, in atrial fibrillation to prevent strokes and thrombosis, as well as for treatment of deep vein thrombosis and pulmonary embolism. Contraindications include active bleeding, serious liver pathology, and allergic reactions to the drug.

Special Use Cases: This research trial, conducted from
2013 to 2017, focused on the efficacy of low-dose rivaroxaban in patients with chronic heart failure and coronary artery atherosclerosis. Of 5022 patients randomly allocated between receiving rivaroxaban and placebo at 628 centres in 32 countries, characteristics and therapy were balanced across groups at the start of testing.

The results did not support a benefit of rivaroxaban (2.5 mg twice daily) in reducing the risk of the composite outcome of death from any cause, myocardial infarction or stroke, compared with placebo. There was no significant difference between groups with regard to the safety of taking the drug - there were no significant differences in the risk of critical bleeding or bleeding resulting in disability. Importantly, hospitalisation due to heart failure was the most frequent event in this study and it is likely that this, rather than death from atherothrombotic events, accounted for a significant proportion of all deaths.

Previous studies have hinted at the potential benefits of rivaroxaban in patients with heart failure, but the results of this trial suggest that thrombin-induced events may not be the major cause of cardiovascular complications in patients hospitalised due to heart failure. Thus, low-dose rivaroxaban added to standard therapy had no significant effect on outcomes of cardiovascular events.

These results highlight the importance of conducting further studies to better understand the mechanisms underlying cardiovascular complications in patients with chronic heart failure and to identify optimal treatment strategies. Experts will need to analyse and expand the understanding of the impact of anticoagulants on major events in this patient population to improve outcomes and enable better clinical practice.

The study of the efficacy of rivaroxaban in combination with aspirin in patients with heart failure (HF) represents a significant moment in the understanding of therapeutic approaches for this pathology. Analysis of the results showed that this combination therapy significantly reduced the risk of cardiovascular complications, including death, myocardial infarction and stroke. A particularly pronounced risk reduction was observed in patients with preserved left
ventricular ejection fraction, where the risk was reduced by 32%, compared to 21% in patients without HF.

This study holds promise for more effective therapy in patients with HF. The combination of rivaroxaban with aspirin may become a key element in the treatment strategy for this population, providing physicians with additional options to reduce cardiovascular complications.

Interestingly, these results are particularly relevant for patients with preserved left ventricular ejection fraction, as existing therapies for this group appear to be less effective. This study provides a new perspective on treatment options for heart failure and may change clinical practice by directing attention to the combination of rivaroxaban with aspirin in the treatment of HF.

**Conclusion:**

In concluding this article on the use of dabigatran and rivaroxaban in patients with heart failure, it is important to highlight the evolution of our knowledge and understanding in the pharmacotherapy of this disease. Recent studies encompassing these new classes of drugs bring important nuances and perspectives to improving quality of life and clinical outcomes in patients with HF.

One key finding is that although dabigatran and rivaroxaban represent meaningful potential to improve the prognosis of patients with HF, the role of these drugs in the context of this disease requires further research. Despite the presumed efficacy and benefits of these DOACs, there is a need to better investigate their impact on clinical outcomes, including not only reducing the risk of cardiovascular complications but also improving patients' quality of life and overall life expectancy.

This review highlights the importance of a more individualised approach to the use of dabigatran and rivaroxaban in patients with HF, taking into account their specific characteristics, comorbidities and risks associated with the use of these drugs. The realisation that these new anticoagulants may play a key role in reducing cardiovascular complications in subgroups of patients with certain characteristics suggests a reconsideration of existing treatment strategies and highlights the need for a
personalised approach in medical practice.

It is important to pay attention not only to the efficacy of these drugs but also to their safety. The lack of specific antidotes for dabigatran and rivaroxaban emphasises the importance of continuous monitoring and assessment of bleeding risk in patients receiving these drugs.

Despite some study limitations, there is a general understanding of the potential of dabigatran and rivaroxaban in the management of HF, which encourages new studies and additional clinical trials to further expand our knowledge of the role of these drugs in improving the prognosis and quality of life of patients with heart failure.

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