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Analysis of the therapeutic effect and application of anticoagulant drugs

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Abstract. As the global population ages, the incidence of cardiovascular disease, stroke, and other diseases associated with thrombosis is also increasing, resulting in a great need for effective anticoagulant treatments. The purpose of this research is to summarize the development of anticoagulant drugs to date, including their drug types, version iterations, mechanisms of action, as well as current challenges and future development directions of anticoagulant drugs. The research will first review traditional anticoagulants, such as vitamin K antagonists and heparins, and discuss in detail their effects, advantages, and limitations. Next, it will give a detailed description of new anticoagulants, such as direct acting oral anticoagulants (DOACs), and analyse their advantages over traditional anticoagulants in terms of safety and efficacy. Finally, it will propose the strategy of individualized therapy for specific population and the combination therapy of anticoagulant therapy and other drugs, and look forward to the development of new anticoagulant drugs in the future. The application of anticoagulant drugs in medicine has a wide range of clinical significance. With the continuous deepening of research, new therapeutic strategies and drugs are constantly being developed and improved, aiming at providing more safe and effective anticoagulant therapy.

Keywords: Anticoagulants, Mechanisms, Application.

1. Introduction

Blood clots have long been a problem for people. If not treated professionally, blood clots may lead to related cardiovascular diseases, which seriously affect people's life and health. Therefore, the study of anticoagulant drugs is particularly important. As the source of life of the body, blood is not only responsible for transporting oxygen and nutrients, but also carries out a series of physiological and immune functions. In some cases, such as genetic predisposition, age, lifestyle, or certain medical conditions, blood may clot prematurely or excessively, leading to the formation of blood clots. Clots can block blood flow and cause tissue ischemia. The condition can lead to a heart attack, stroke or deep vein thrombosis, posing a serious threat to life.

In order to prevent and treat diseases related to thrombosis, anticoagulant drugs are widely used in clinical practice. This class of drugs can reduce the likelihood of blood clotting, thereby preventing or treating diseases associated with blood clots. For blood clots that have already formed, anticoagulant drugs can also help reduce the risk that they will continue to grow. With the deepening of medical research, the understanding of thrombus is gradually deepened. The original understanding of anticoagulant therapy was limited to a single mechanism and drug, but now we have a range of

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anticoagulants with different mechanisms and indications. The earliest anticoagulants, such as traditional heparin and warfarin, were effective in reducing the risk of blood clots, but their use was subject to many limitations, such as dose adjustment, interactions between food and drugs, and bleeding risk. In recent years, the emergence of new oral anticoagulants (NOACs/DOACs) has brought revolutionary changes to anticoagulant therapy. These drugs directly target specific thrombin or factors and have faster onset times, fewer food and drug interactions, and more predictable efficacy. They have been shown in several large clinical trials to be equal to or better than traditional anticoagulants, while having a lower risk of bleeding.

2. Application of anticoagulant drugs

2.1. Development history

Early traditional anticoagulant drugs are mainly divided into two categories: vitamin K antagonists and heparin anticoagulants. The origin of the vitamin K antagonist represented by warfarin is the "biscoumarin" isolated from the corrupt clover, and according to the relevant data, researchers eventually synthesized warfarin and other drugs. Vitamin K in the human body promotes carboxylation of certain Gla residues at the ends of prothrombin molecules, increasing their ability to bind to Ca^{2+}, and linking to phospholipid surfaces and conjunctiins, thus having clotting activity [1]. However, when vitamin antagonists are applied, only uncarboxylated glutamic acid residues are produced in hepatocytes, and this immature prothrombin cannot bind to Ca^{2+} and has no coagulation function, thus prolongating the coagulation time and achieving the anticoagulation effect [1].

Heparin anticoagulants are mainly divided into ordinary heparin and low molecular weight heparin. John Mclean of John Hopkins University in the United States first discovered common heparin (ungraded heparin, UFH) and used it in the clinic as an anticoagulant in 1934. Low molecular weight heparin (LMWH) is a small molecular weight heparin fragment obtained by enzyme depolymerization or chemical method on the basis of ordinary heparin. Compared with ordinary heparin, low molecular weight heparin has stronger antithrombotic effect and weaker anticoagulation effect, which greatly reduces the risk of bleeding. The relative molecular weight of low molecular weight heparin is smaller than that of ordinary heparin, and it can only bind to antithrombin III, but not to IIa, so it has an anti- x A effect [2]. Because IIa activity is the main index of anticoagulation, low molecular weight heparin has weak anticoagulation effect. In addition, activation of thrombin is one of the primary causes of thrombosis. Low molecular weight heparin has a potent anti-xA action, which can prevent thrombin activation and hence have an anti-thrombotic effect [3].

Direct thrombin inhibitors, direct factor Xa inhibitors, and antiplatelet medicines are the principal novel anticoagulant medications available today. Direct thrombin inhibitors (DTIs) are anticipated to take the role of vitamin K antagonists in anticoagulant therapy because they have the ability to inhibit thrombin and prevent the interaction between thrombin and fibrin. This allows them to overcome the limitation of the heparin antithrombin complex's inability to inactivate thrombin. DTIs is generally composed of dozens of amino acids. According to the different binding modes with thrombin, DTIs can be divided into bivalent DTIs and monovalent DTIs. The former first binds the acidic amino acid at the C-end to the alkaline site of thrombin to block the substrate recognition site of thrombin, and then binds the N-end to the active center of thrombin. Thus, the catalytic activity of thrombin is inhibited, and the latter only binds to the active site of thrombin [4].

Factor Xa is a serine protease, which can convert prothrombin into thrombin and is a direct inhibitor of factor Xa [5]. Direct inhibitors of factor Xa can achieve anticoagulant effect by inhibiting factor Xa. Moreover, inhibiting factor X a at the source can maintain the normal physiological hemostasis process of the human body and effectively reduce the risk of bleeding [5]. Rivaroxaban, a representative drug of direct coagulation Xa inhibitors, can be used to lower the risk of recurrent acute coronary syndrome (ACS), prevent stroke and non-central nervous system embolism in patients with non-valvular AF, in addition to preventing deep vein thrombosis and pulmonary embolism in patients who have had hip or knee replacement surgery. In June 2009, it received permission to enter China. 14264 AF patients from

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1178 sites in 45 different countries who had at least two stroke risk factors were included in the ROCKET AF trial, which looked at the efficacy and safety of rivaroxaban in preventing stroke and non-central nervous system systemic embolism in people with nonvalvular AF [6]. Ninety percent of patients with a CHADS2 score below three were randomly assigned to take either rivaroxaban (20 mg/day) or warfarin. The results of treatment intention population analysis showed that the annual incidence of the primary endpoint (stroke and systemic thrombosis) in the rivaroxaban group was 2.1%, which was not worse than 2.4% in the warfarin group (P=0.12), but the incidence of the primary endpoint during treatment was 1.7% and 2.2% in the 2 groups, respectively, and rivaroxaban was better than warfarin. Relative risk was reduced by 21% (P=0.02). The study also found that the incidence of rivaroxaban in hemorrhagic stroke was 0.3%, significantly lower than 0.4% in warfarin. The composite end point incidence of major bleeding and clinically relevant non-major bleeding was 14.9% for rivaroxaban, comparable to 14.5% for warfarin, while critical site bleeding, fatal bleeding, and intracranial hemorrhage were significantly reduced. The incidence of myocardial infarction was similar between the two groups (0.9% for rivaroxaban vs. 1.1% for warfarin) and the liver safety was similar between the two groups [6]. Based on the results, the US Food and Drug Administration (FDA) approved its marketing in November 2011 for the prevention of AF stroke [7]. After rivaroxaban (Figure 1), the first direct inhibitor of coagulation Xa factor listed in 2009, Apixaban, Edoxaban, Betrixaban, Omisaban and Rezaxaban were successively introduced, adding new options for anticoagulation therapy.

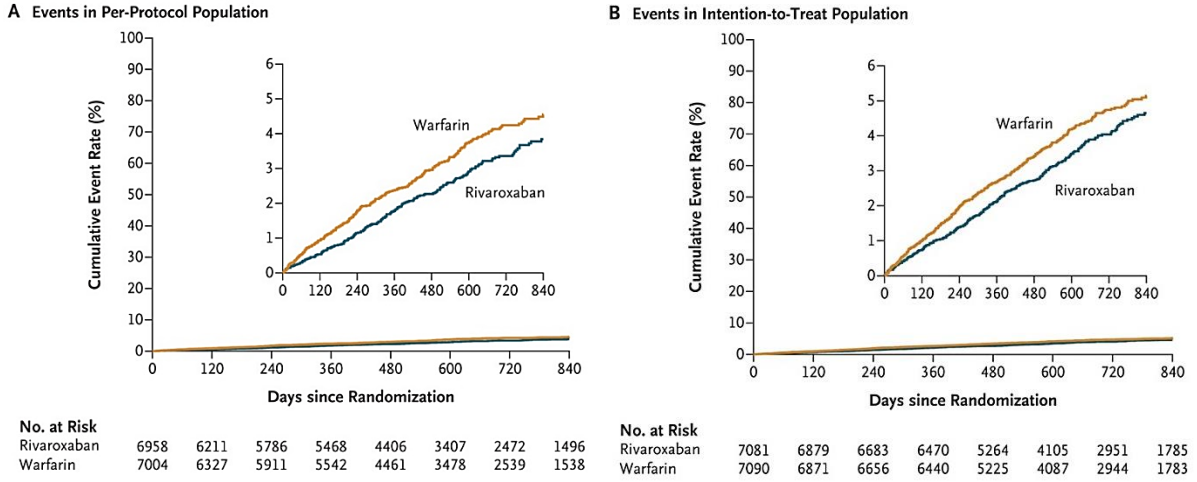

Figure 1. Cumulative rate of primary endpoints in the treatment population [7].

Antiplatelet drugs are developed for all aspects of platelet activation and related targets, and can act on all stages of platelet activation, adhesion, and aggregation. The most commonly used antiplatelet drug is aspirin. Aspirin, a cycoperoxidase (COX) inhibitor, can encourage the acetylation of serine 529 at the COX-1 active site, irreversibly inhibit COX-1 activity, and reduce the production of TXA2, a potent platelet polymerizer that ultimately influences the aggregation and release of platelets. Thus, the anticoagulation effect is achieved. Aspirin and clopidogrel are the representative drugs. A random number table approach was used to split 141 individuals with latent coronary heart disease into groups A, B, and C in one investigation. Group A was given clopidogrel orally, 75 mg/ time, once/day, for 8 weeks. Group B was given aspirin enteric-coated tablets orally, 100 mg/ time, once/day, for 8 weeks. Group C was given clopidogrel combined with aspirin maintenance treatment, and the drug administration method was the same as group A and group B, and relevant data were tested on time [8].

According to the study's findings, using clopidogrel together with aspirin can greatly boost the antiplatelet impact in individuals with concealed coronary heart disease who are receiving maintenance therapy. The platelet aggregation rate, maximal aggregation rate, and platelet count of group C after treatment were considerably lower than before treatment, group A and group B. The overall effective

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rate of group C was significantly greater than that of groups A and B. Inhibiting platelet aggregation can lessen inflammatory mediator release, lessen vascular intima damage, successfully stop atherosclerosis from progressing, and enhance therapeutic efficacy. Although the platelet count is reduced, it is still in the normal range [8]. Such antiplatelet drugs have penetrated into our daily life treatment and made great contributions to the field of anticoagulation.

2.2. Limitations

At present, the mainstream anticoagulant drugs still have some side effects and defects. Vitamin K antagonists represented by warfarin in traditional medicines may cause severe vascular calcification, especially in patients with high blood pressure and diabetes. Vascular calcification can lead to increased stiffness and reduced compliance of blood vessel walls, and is an important risk factor for cardiovascular diseases [1]. Many experiments have shown that vitamin K inhibitors (VKA) can cause vascular calcification. Howe et al. showed severe media calcification 6 weeks after VKA was administered to mice [9]. Heparin drugs may cause more adverse reactions such as bleeding, allergic reaction, heparin-hyperkalemia, thrombocytopenia and other symptoms during the treatment of heparin drugs [10]. Although low molecular weight heparin has greatly reduced side effects, it is still necessary to be cautious when using it.

As for the new anticoagulant drugs, side effects have been greatly reduced, but they are still not negligible. Among the direct inhibitors of factor Xa, rivaroxaban and apixaban are associated with severe bleeding, anemia (including postoperative anemia and wound bleeding), decreased platelet count and other adverse reactions [5]. After the start of treatment, patients should be closely monitored for bleeding complications, which can be achieved by measuring hemoglobin at regular intervals. Rivaroxaban orally is metabolized by the liver and has a certain effect on liver function. In an analysis of safety studies, hepatotoxicity was compared between rivaroxaban and warfarin in 604 patients [11]. Moreover, the treatment of such drugs is expensive, and patients need to choose carefully. Direct thrombin inhibitors take hirudin as an example. Compared with heparin, hirudin is better than heparin in anticoagulation, assisted thrombolysis and interventional therapy for unstable angina pectoris, and may play a key role in improving the prognosis of high-risk patients. However, compared with heparin, hirudin has a higher relative risk of bleeding, and the relationship between its efficacy and safety has not been clearly defined, and its clinical application is limited [4]. Among the antiplatelet drugs, aspirin has been widely concerned as a daily drug. However, there are also the following problems in the application of aspirin: gastrointestinal injury, aspirin asthma and aspirin resistance. Gastrointestinal damage caused by aspirin can include ulcers, bleeding and even perforation. It is thought that aspirin may mainly affect the defense function of the gastrointestinal mucosa. Patients who develop asthma within minutes or hours of taking aspirin are known as aspirin asthma. Aspirin asthma may lead to more serious adverse consequences, especially in people with allergies, there is a risk of death.

To sum up the above views, the side effects of anticoagulant drugs in the treatment process are unavoidable, but in the process of drug law, these side effects are gradually alleviated, and there are substitute drugs, patients need to use drugs reasonably under the guidance of doctors to achieve the best results.

2.3. Future development direction

Although several novel oral anticoagulants such as macromolecular anticoagulants, direct thrombin inhibitors (e.g. dabigatrun), and direct factor Xa inhibitors (e.g. rivaroxaban and apicaban) are available, new specific anticoagulants should be explored to provide better efficacy and fewer side effects, especially to reduce the risk of bleeding while maintaining efficacy. Reversible drugs can also be studied to prepare specific antidotes that can quickly reverse the effects of drugs and reduce the risk of bleeding. Genetic testing and other biomarkers may help doctors more accurately select and tailor anticoagulant therapies for patients, ensuring they are both effective and safe. For example, it is the function of the liver and kidneys may decline, leading to changes in the metabolism and excretion of drugs. As a result, older patients may need to adjust their medication dose or choose a different medication. Children's

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bodies are developing, so they may respond differently to drugs than adults. Drug therapy in children requires specific dosages, routes of administration, and drug forms. Patients with multiple complications may need to be treated with multiple medications, so doctors need to consider interactions between medications and adjust the treatment plan. For combination therapies, certain conditions or disease states may benefit from a combination of multiple anticoagulant strategies. For example, in some cases, a combination of an anticoagulant drug with an antiplatelet drug may provide better protection.

3. Conclusion

Over the past few decades, anticoagulant drugs have played a vital role in the prevention and treatment of cardiovascular disease. From traditional warfarin to novel direct thrombin inhibitors and factor Xa inhibitors, each drug has its own unique pharmacological mechanisms, application areas, and potential risks. Future research may focus on reducing the bleeding risk of these drugs, improving their therapeutic effectiveness, discovering new mechanisms of action, and exploring combinations with other drugs or treatments. Individualized treatment strategies are also particularly important for specific patient groups, such as the elderly, children, pregnant women, and patients with specific genotypes. For clinicians, understanding the latest advancements in anticoagulant therapy, possible risks and potential drug interactions, as well as communicating with patients to ensure they are using their medication correctly, are key to ensuring treatment effectiveness. With the advancement of personalized medicine, we also look forward to the selection and adjustment of more precise anticoagulant therapy based on the patient's genetics, lifestyle and complications. In conclusion, the importance of anticoagulants in clinical practice continues to grow, but the selection of appropriate drugs and dosages still requires a comprehensive consideration of patient characteristics and needs. In the development of new drugs and the practice of existing drugs, the medical community needs to remain vigilant and constantly pursue better treatment strategies and outcomes.

References

[1] Fu K, Liu J 2013 Chinese Journal of Interventional Cardiology 195-198
[2] Yin C, Yanlei Y, Xinyue L, et al. 2018 Journal of Pharmaceutical Sciences 107(5) 1290-1295
[3] Pannucci C, Fleming K, Bertolaccini C, et al. 2019 JAMA surgery 154(8) 697-704
[4] Meng B, Lu C, Jiang Y 2006 Chinese Journal of Cardiovascular Research 72-75
[5] Zhang S 2013 Evaluation and Analysis of Drug-Use in Hospitals of China 782-786
[6] Rocket AF 2010 Am Heart J 2010 159(3) 340-347
[7] Patel MR, Mahaffey KW, Garg J, et al. 2011 N Engl J Med 365(10) 883-891
[8] Neng C, Chang S 2021 Chronic Pathology Journal 1808-1812
[9] Howe AM, Webster WS. 2000 Int J Exp Pathol 81 51-56
[10] Wang W 2001 Clinical Medicine 39-40
[11] Eriksson BI, Borris LC, Dahl OE, et al. 2006 Circulation 114(22) 2374-2381