REVIEW

A Literature Review of Antithrombotic Therapy for Patients of Venous Thromboembolic Events with Comorbidity of Coronary Heart Disease

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Abstract Patients with venous thromboembolism (VTE) and concurrent coronary heart disease (CHD) are not rare in clinic. The main challenge in the treatment for these patients is that the antithrombotic therapies for VTE and CHD are different from each other, but the combination of the two therapeutic strategies would increase the risk of bleeding. There is a need to optimize the antithrombotic therapeutic scheme on the basis of individual conditional, in order to balance the therapeutic effects and the bleeding risk. This article discussed the appropriate antithrombotic therapy when balancing the effectiveness and the risk in different circumstance of concurrence of VTE and CHD, such as combining anticoagulation therapy, dual antiplatelet therapy (DAPT), triple antithrombotic therapy (TAT), thrombolytic therapy and extending therapy, in order to provide safe, standard and effective therapeutic schemes for the clinical management of these patients. In the meantime, this article also provides perspectives regarding the application of novel non-vitamin K anticoagulants (NOACs) and the assessment tools of bleeding risk.

BOTH venous thromboembolism (VTE) and coronary heart disease (CHD) are common conditions in the modern medicine. The deep venous thrombosis (DVT) and pulmonary embolism (PE), the main clinical types of VTE, oc-

cur in 17.1 and 3.9 per 100 000 respectively annually in China,¹ and these numbers may be higher in Europe and America.^{2,3} CHD, including chronic coronary artery disease (CAD) and acute coronary syndrome (ACS), has been the leading cause of death in developed countries,⁴ and China is not an exception. In 2014, the Chinese rural mortality of heart disease is 143.72 per 100 000, while the urban mortality is 261.99 per 100 000.⁵ Nevertheless, the accurate prevalence data of patients of VTE with concurrent CHD are still lacking, though some studies^{6,7} have indicated that these patients are not unusual in clinic.

However, VTE and CHD have been considered

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separately as two entities for a long time, mainly because of their different anatomy and mechanism of thrombosis. Arterial thrombosis, the main cause of CHD, is largely a matter of activation of platelet, whereas venous thrombosis is mainly an activation of clotting system. Correspondingly, the basic therapy for arterial thrombosis is using antiplatelet drugs, while for venous thrombosis, it would be essential to choose a proper anticoagulants among a variety of anticoagulants. Neither antiplatelet nor anticoagulant therapy alone is effective enough to cure the patients with VTE and concurrent CHD completely; however, combining antiplatelet therapy with anticoagulants would absolutely raise the risk of hemorrhage.

Recently, some studies suggested that the mechanisms of the two diseases may not as different as we had thought. They possibly share common risk factors,⁸⁻¹¹ and even there may be a causal relationship, or they might be the risk factor to each other.¹²⁻¹⁴ These considerations lay the foundation of optimizing the strategy of the conjunctive therapy.

Combination therapies for VTE Concurrent with stable CHD

According to the Chinese guideline published in 2016,¹⁵ for the patients of PE concurrent with stable CHD (stable angina pectoris, ischemic cardiomyopathy, or latent coronary heart disease), the anticoagulation treatment is the combination of parenteral and oral anticoagulation (OAC), which is the same as for PE alone. This is in agreement with some Chinese experts,¹⁶ though there are no evidence-based data to support or contradict it. A specific usage in line with European Society of Cardiology (ESC) guidelines¹⁷ is that using parenteral anticoagulation immediately while waiting for the results of diagnostic tests that are to confirm the risk of PE and to decide whether thrombolytic therapy is necessary, meanwhile initiating oral anticoagulation therapy as soon as possible, best on the same day.

But so far, there hasn't been a unanimous standard for the combination of parenteral and oral anticoagulation as an appropriate treatment for the discussed patients. Castellucci *et al*¹⁸ published a careful systemic review and meta-analysis, which compared several combinations of parenteral plus oral anticoagulation therapies that were frequently used, and suggested that unfractionated heparin-vitamin K anticoagulants (UFH-VKA) combination may be the least effective, rivaroxaban or apixaban may have the

lowest risk of hemorrhage, and low molecular weight heparin-vitamin K anticoagulants (LMWH-VKA) combination has no significant difference from the other combinations in terms of the safety and effectiveness. These findings made the LMWH-VKA a better choice, with rivaroxaban or apixaban as an alternative to VKA. Both rivaroxaban and apixaban are novel non-vitamin K anticoagulants (NOACs), and have been found equal or superior to VKAs not only in effectiveness but also in safety in recent years.¹⁹ This has made them the first recommendation by American College of Chest Physicians (ACCP).²⁰ The advantages of NOACs, as listed in detail in an article by Verdecchia *et al*,²¹ included lower risks of hemorrhagic stroke, intracranial bleeding and thromboembolism, stable international normalized ratio (INR) control, fewer interactions with drugs and food, etc. In spite of these advantages, not all NOACs are proper to replace VKAs for patients with VTE concurrent with CHD. A study has pointed out that among those promising agents, dabigatran increases the risk of myocardial infarction (MI), while apixaban decreased the risk of both arterial and venous thrombotic events.²² Consequently, carefully choosing a NOAC is deserved when using parenteral plus oral anticoagulation as joint scheme.

Triple antithrombotic therapies for VTE concurrent with ACS (except for STEMI)

The most frequently recommended and used therapeutic scheme in clinics is triple antithrombotic therapy (TAT) for patients with DVT or those at low-risk of PE (defined as normal blood pressure and have neither heart dysfunction nor elevated biomarkers) and concurrent acute coronary syndrome (ACS), with exception of ST-segment elevation myocardial infarction (STEMI). The TAT consists of a dual antiplatelet therapy (DAPT) and an OAC. To be specific, the TAT mostly refers to applying VKA (INR 2.0–2.5), aspirin (100 mg/d) and clopidogrel (75 mg/d), with one of NOACs as an alternative to the VKA (rivaroxaban: 15 mg twice daily for 3 weeks, followed by 20 mg once daily; or apixaban: 10 mg twice daily for 7 days, followed by 5 mg twice daily; or dabigatran: 150 mg or 110 mg twice daily for people older than 80 years old) for 3 months.^{15, 17}

However, there are little data to support the utility of TAT for the discussed patients, resulting in the lack of precise recommendations in guidelines on this issue. Meanwhile, the apparent increase of major bleeding caused by TAT has also restricted its applica-

tion, though replacing warfarin with an NOAC may be a bit better.^{23, 24} A review of randomized control trials by Jeremy *et al*²⁵ indicated that for ACS patients, rivaroxaban or apixaban plus DAPT contributed to a small reduction of ischemic events, but increased the bleeding risk obviously. This review also pointed out that if choosing TAT, it is important to monitor INR carefully and shorten the duration of medication time.

Thrombolytic therapies once PE or STEMI happens

For patients who have either STEMI or high-risk PE (defined as acute pulmonary embolism that systolic blood pressure is below 90 mmHg, or systolic pressure has dropped by at least 40 mmHg for more than 15 minutes), the first choice of treatment is prompt thrombolysis as long as there is no contraindication, which has been included in a Chinese guideline.¹⁵ Particularly, when high-risk PE and STEMI happens simultaneously, thrombolytic therapy is definitely utile to restore the perfusion of both coronary artery and pulmonary artery.

However, for patients who is at intermediate-risk of PE (defined as preserved systolic blood pressure with dysfunction of right ventricle on echocardiography and/or elevated cardiac biomarkers), it is still controversial whether thrombolysis is appropriate or not. Recently, Sanchez *et al*²⁶ carefully analyzed several randomized trials and concluded that for intermediate-risk PE, thrombolytic therapy should be considered only when the patient is under 75 years old and at low risk of bleeding. In term of the dangerousness, a multicentric randomized controlled trial performed by Chen Wang *et al*²⁷ compared the validity and safety of a full-dose recombinant tissue-type plasminogen activator (rt-PA) with a half-dose rt-PA, coming to a verdict that the half-dose rt-PA had a lower bleeding risk (3% versus 10%), while their effects were parallel. The Moderate Pulmonary Embolism Treated with Thrombolysis trial²⁸ reached a similar conclusion that the "safe dose" of rt-PA was effective and safe. Yet the prognosis of intermediate-risk PE is not as poor as high-risk PE, so it is deserved to weigh the benefit of using thrombolytic therapy verse its risk of bleeding in this situation. More high-quality evidence-based data and population-based clinical trials are still needed.

In situation that a patient of STEMI has received percutaneous coronary intervention (PCI), which should not be put in the first place if there is no need of urgent stent implantation,¹⁵ combination of anti-

thrombotic therapy should be considered. A study by DeEugenio *et al*²⁹ which enrolled 97 patients revealed that warfarin was an independent predictor of major bleeding. Since neither OAC nor DAPT is sufficient to cure the concurrence of STEMI and VTE, none of them is recommended to be a substitute of TAT.³⁰ Thereby in the guidelines it is recommended that TAT should be used but with a shortened medication time of 2-4 weeks,¹⁵ because short-term usage of TAT yield an acceptable bleeding risk. Another essay by Khurram *et al*³¹ put a more concrete and rational advice, which was choosing therapeutic scheme according to the patients' risks of bleeding. For patients at low or mediate risk of bleeding, TAT is the best option; for patients at high-risk of bleeding, warfarin plus clopidogrel should be considered. Another review has also concluded that the effect of VKA plus clopidogrel were comparable with the TAT, but was superior to the other strategies.²³ Warfarin plus aspirin was also demonstrated as an acceptable treatment by a meta-analysis³² and a piece of literature.¹⁶

Rivaroxaban is the first and the only NOAC by far that has been supported by RCTs data on patients with atrial fibrillation (AF) who have undergone PCI. It has attracted an extensive interest, because its complications has been far beyond our expectation. A recent study by Gibson *et al*³³ which involved 2124 participants who had AF and had undergone PCI is quiet impressing. The patients were divided into two groups, one group was administrated rivaroxaban (15 mg once daily) plus P2Y₁₂ inhibitor for 12 months, the other was administrated rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months. Both groups had significant lower bleeding rates than the group adopting standard therapy (VKA plus DAPT), while their efficacy rates were similar. In this study, the author also mentioned that for patients who were receiving DAPT because of ACS, a very low dose of rivaroxaban (2.5 mg twice daily) plus DAPT would reduce the death rates caused by cardiovascular diseases, MI and stroke. These outcome data were valuable for the consideration of adopting a low dose of rivaroxaban plus DAPT in the clinical management of patients who have VTE and are about to undergo PCI, since the therapy for these patients also includes anticoagulation and antiplatelet. More researches and evidence-based data are needed in this area.

Extending therapy

For patients with VTE, OAC is admitted as the tradi-

tional extending therapy, primarily including one of NOACs or warfarin for at least 3 months; while for CHD patients, aspirin can be administered for a lifelong time as the extending therapy. Some Chinese scholars proposed that the extending therapy should use warfarin or other oral anticoagulants, but they also come up with that aspirin may be benefit to VTE patients. For patients who are reluctant to use warfarin or have discontinued anticoagulant therapy, they can use aspirin alternatively.^{15, 16} A literature review by Mekaj *et al*³⁴ emphasized that aspirin had effectiveness in prevention and treatment of both VTE and CHD. Becattini *et al*³⁵ performed a study involving 402 patients and concluded that using aspirin for long-term therapy decreased the recurrence rate of VTE (5.9% versus 11%), with no increase of major bleeding rate. Though in another study by Brighton *et al*, the decline of the recurrent VTE was not statistically significant,³⁶ both studies had affirmed the validity of employing aspirin in extending therapy.

Assessment of bleeding risk

In the process of antithrombotic therapy for patients with both VTE and CHD, it is critical to assess bleeding risks of patients individually. At present, there are several clinical prediction scales, such as the Kuijer,³⁷ RIETE,³⁸ HAS-BLED,³⁹ ATRIA,⁴⁰ HEMORR2HAGES⁴¹ and ACCP.⁴² However, the predictive values of these scales from limited studies were not satisfied enough and their discriminatory performances were regarded to be poor.⁴³⁻⁴⁵ Another study also pointed out that among a variety of bleeding risk estimation tools, none has been supported by evidence-based data.⁴⁶ Studies suggested that HAS-BLED may be a good choice for the assessment of bleeding risk of patient with AF and is undergoing anticoagulation therapy.⁴⁷⁻⁵⁰ But for patients who have had PCI and need short- or long-term DAPT, Costa *et al*⁵¹ suggested that CRUSADE performed better than HAS-BLED in predicting major bleeding. This situation has also pointed out a direction for profound research in future.

Conclusions

In clinical management of patients with VTE and concurrent CHD, it is crucial to balance the effect and risk according to the individual situation when choosing the proper therapeutic scheme. For patients with VTE and stable CHD, LMWH-VKA may be the most available treatment, and a proper NOAC as an alternate to VKA

may be more beneficial. Although NOACs are promising agents, evidence-based data are still needed to identify their indications. Whether TAT is proper for patients with VTE and ACS except for STEMI is still unknown; once TAT is applied, monitoring INR carefully and shortening therapeutic duration time are needed. Thrombolytic therapy should be used for high-risk PE patients with STEMI, while the treatment for intermediate-risk PE patients is still in dispute. For STEMI patients who have received PCI, the proper therapy should be based on their individual bleeding risk, of which the effective assessment methods are still lacking and more investigations are needed.

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