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Meta-analysis

Efficacy and safety of novel oral anticoagulants versus vitamin K antagonists in the treatment of venous thromboembolism

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Abstract

The aim of this meta-analysis was to systematically evaluate the efficacy and safety of novel oral anticoagulants and vitamin K antagonists in the treatment of venous thromboembolism. A total of 6 studies met the inclusion criteria and a total of 19,350 patients with venous thromboembolism were included. Among them, rivaroxaban (3 RCTs, n=90/3,449/4,832); dabigatran (2 RCTs, n=200/2,539); edoxaban (1 RCT, n=8,240). The results of meta-analysis showed that the total bleeding rate after treatment with the vitamin K antagonist group was higher than with the new oral anticoagulant group (OR=0.82, 95% confidence interval 0.75-0.90, p<0.0001), and the difference was highly statistically significant. Overall, new oral anticoagulants are comparable to vitamin K antagonists, but new oral anticoagulants can reduce the occurrence of bleeding events and the safety was superior to vitamin K antagonists.

Introduction

Venous thromboembolism refers to the abnormal coagulation of blood in the vein, causing partial or complete obstruction of the lumen. It includes deep venous thrombosis and pulmonary embolism, which are the manifestation forms of the same disease at different stages. It is frequently seen in long-term bedridden and perioperative complications.

Venous thromboembolism is the third leading cause of death induced by circulation system disease, which is only second to myocardial infarction and stroke, and the incidence increases sharply with age, with an annual incidence of 100–300 per 100,000 inhabitants (Mackman, 2008; Mazzolai et al., 2017; Imberti et al., 2018).

Venous thromboembolism is associated with substantial mortality and it also tends to recur, with a recurrence risk as high as 30% within 5 years after cessation of anticoagulation (Kyrle and Eichinger, 2012). The early clinical confirmation of deep venous thrombosis and pulmonary embolism depends on the high understanding of clinicians and the public towards these diseases. A latest comprehensive survey indicated that, the clinical consciousness of venous thromboembolism in Asian countries was universally low (Angchaisuksiri, 2011). Therefore, it is necessary to more accurately identify patient associated with the risk of venous thromboembolism, and safe and effective preventive treatment are also needed.

Anticoagulant therapy is the effective treatment for venous thromboembolism, which can prevent its recurrence and the incidence of death event. Warfarin, a kind of vitamin K antagonist, has been the cornerstone

of treatment for venous thromboembolism patients since 1950s, which is the most commonly used oral anticoagulant (Holbrook et al., 2005). Warfarin is a coumarin anticoagulant, which can suppress the synthesis of vitamin K-dependent coagulation factors (including II, VII, IX and X) to exert the anticoagulant effect. It is cheap in price and has definite effect. As a result, it has been extensively applied in clinical anticoagulant treatment. Reversal of the anticoagulation of warfarin can be achieved through administration of vitamin K or transfusion of coagulation factors. However, the safety and effectiveness of warfarin treatment mainly depend on whether the international normalized ratio is maintained within the treatment range. Nonetheless, the treatment window of oral administration of warfarin is narrow, and the international normalized ratio level of median effective dose is only twice of that of median lethal dose. Therefore, it requires to frequently collect blood to monitor international normalized ratio and may require to repeatedly adjust the dose. Moreover, warfarin exerts its anticoagulation through antagonizing vitamin K, and most foods (such as carrot, broccoli, animal livers and green vegetables) containing a large amount of vitamin K will reduce the anticoagulation of warfarin.

In contrast, foods like grapefruit, cod-liver oil, gingko and the root of red-rooted salvia will enhance the anticoagulation of warfarin. Besides, many medicines will also affect the anticoagulation of warfarin, for example, when amiodarone is used in combination with warfarin, it will increase its anticoagulant effect (Mega and Simon, 2015). Therefore, vitamin K antagonists have narrow treatment window regardless of their low price, which require frequent monitoring, can interact with medicines and foods, and may lead to poor compliance. It may pose a great obstacle for some populations, such as the elderly. Some hospitals even set up the anticoagulant clinic to guide patients to use warfarin, which has demonstrated the complexity of clinical application of vitamin K antagonists. Fortunately, some new oral anticoagulants (NOACs) emerge and have been introduced in China, which can achieve the similar therapeutic effects of vitamin K antagonists but will not induce the risk of bleeding due to overdose. Typically, 4 NOACs have been approved by the Food and Drug Administration and European Medicines Agency to be used in venous thromboembolism, which are dabigatran, rivaroxaban, apixaban and edoxaban (Vora et al., 2016; Moreno et al., 2017). NOACs do not require frequent monitoring and have a few medicine and food interactions. They can provide the predictable anticoagulation through fixed doses, which facilitates perioperative management. However, NOACs are associated with the problems of poor compliance in the absence of monitoring, costly, risk of bleeding and lack of specific antagonists. Besides, the evidence-based medical evidence is lacking in China at present. The venous thromboembolism antithrombotic treatment guideline released by the American Collage of Chest Physicians in 2016 had recommended NOACs (grade 2B) rather than vitamin K antagonists anticoagulants for the anticoagulant treatment for deep venous thrombosis and pulmonary embolism patients (with no cancer) (Kearon et al., 2016).

The EINSTEIN randomized clinical trial indicated that, NOACs anticoagulant rivaroxaban was not inferior to vitamin K antagonists in treating and preventing the recurrence of acute venous thromboembolism (Investigators, 2010; Investigators et al., 2012). A large single-center observational study indicated that, when using oral anticoagulants to treat chronic deep venous thrombosis, NOACs had manifested similar efficacy and safety to warfarin (Wakakura et al., 2017). For patients with venous thromboembolism, standard anticoagulation therapy can effectively reduce its incidence and mortality, and reduce the incidence of post-thrombotic syndrome. Achieving optimal clinical outcomes should fully consider the risk of bleeding and thrombosis as well as the individual choice of anticoagulant drugs and duration of anticoagulation, so as to bringing more benefits to patients.

In this study, we had adopted the Cochrane systemic evaluation method for meta-analysis, so as to examine the effectiveness and safety of NOACs and vitamin K antagonists on venous thromboembolism. Meanwhile, we had carried out systemic evaluation and meta-analysis on the existing clinical trial results at home and abroad, with an aim to provide reference for the reasonable application of anticoagulants in clinic.

Materials and Methods

Retrieval strategy

Databases, including PubMed, Google Scholar, Baidu Scholar, Cochrane Library, EMBASE, CBM, CNKI and Wanfang Data, were included through computer to retrieve the randomized controlled trials (RCTs) comparing the effectiveness and safety of NOACs and vitamin K antagonists on venous thromboembolism published at home and abroad. The Chinese retrieval words were “new oral anticoagulants”, “dabigatran”, “rivaroxaban”, “apixaban” and “edoxaban”, “vitamin K antagonists”, “warfarin”, “venous thromboembolism”, “deep venous thrombosis” and “pulmonary embolism”. The English retrieval words were “new oral anticoagulants”, “dabigatran”, “rivaroxaban”, “apixaban” and “edoxaban”, “vitamin K antagonists”, “warfarin”, “venous thromboembolism”, “deep venous thrombosis” and “pulmonary embolism”. At the same time, it is supplemented by manual search of relevant systematic review references. The search deadline is May 20, 2018.

Literature inclusion and exclusion criteria

Inclusion criteria: 1. Study type: RCTs on the effectiveness and safety of NOACs and vitamin K antagonists on treating venous thromboembolism published at home and abroad; 2. Object of study: patients finally diagnosed with venous thromboembolism (including deep venous thrombosis, pulmonary embolism or both) through ultrasonic vascular doppler imaging or CT vascular imaging examination; 3. Intervention measure: The experiment group received NOACs treatment, while the control group underwent vitamin K antagonists treatment, the baseline conditions between experiment group and control group were basically consistent and comparable, and international normalized ratio was regularly monitored, which should be stabilized at 2.0-3.0; 4. Outcome index: Analyzed the differences in indexes such as thrombus recurrence and bleeding event between experiment group and control group.

Exclusion criteria: 1. studies not selecting the above indexes as the outcomes; 2. non-RCTs or studies with unprecise experimental design, repetitive publication and incomplete data; 3. clinical trial studies studying the anticoagulants in other diseases.

Data extraction and quality evaluation

Firstly, read the title and abstract of the literature, and the full-text of the potentially eligible literature was read to determine whether it conformed to the inclusion criteria. All potentially eligible studies were evaluated through the full-texts, Literature was screened by 2 researchers independently according to the pre-established inclusion criteria and exclusion criteria. The related data in studies conforming to the inclusion criteria were entered into the Excel data extraction sheet. The extracted information included 1. patient characteristics: Age and sex ratio; 2. intervention type: type of therapeutic, dosage and measure of administration, and treatment duration; and 3. outcome indexes: Frequency of recurrent venous thromboembolism event and incidence of bleeding event (including severe bleeding event and general bleeding event). Besides, the modified Jada scale was adopted for evaluating the risk of bias for quality evaluation.

Statistical analysis

The RevMan5.3 software was employed for statistical analysis of the collected data. The odds ratio (OR) was used as the effect size of two-category data, and the 95% confidence interval (CI) was calculated. A difference of $p \leq 0.05$ was deemed as statistically significant. Adopted the fixed effect model when the heterogeneity test results were not significantly different ($p \geq 0.1$, $I^2 \leq 50\%$), otherwise the random effect model was used. And use an inverted funnel plot to analyze potential biases.

Results

Literature retrieval and screening results

A total of 1,366 literature was preliminarily retrieved according to the above inclusion and exclusion criteria, 1,313 of them was excluded after reading the titles and abstracts, and the remaining 53 was downloaded and the full-texts were read. 47 out of these 53 literature was excluded, including 11 with irrelevant research objective, 23 reviews, conference papers and critical papers, 10 non-RCTs and 3 repetitive studies. Eventually, a total of 6 literature was screened and enrolled into this study (Schulman et al., 2009; Bauersachs et al., 2010; Buller et al., 2012; Buller et al., 2013; Didi et al., 2017; Ym, 2017) (Figure 1).

Basic characteristics of the enrolled studies and quality evaluation

All the 6 studies enrolled in this paper were RCTs, including 2 Chinese and 4 English literature. Specifically, the Hokusai-venous thromboembolism investigators and Sam Schulman had evaluated the effectiveness and safety of edoxaban and dabigatran over warfarin on treating venous thromboembolism patients, respectively. The EINSTEIN Investigators and EINSTEIN-PE Investigators had compared the efficacy between deep venous thrombosis and pulmonary embolism patients, respectively. Huang Yiming and Sun Didi had evaluated the effects of rivaroxaban and dabigatran on treating venous thromboembolism patients in China. In all the enrolled studies, the thrombus recurrence rate during treatment was used as the efficacy outcome index, while the incidence of bleeding event during treatment was the safety outcome index. The sample sizes were different among different studies. Typically, the sample size was the greatest in the study by the Hokusai-venous thromboembolism investigators (n=8,240), while that was the smallest in the study by Huang Yiming (n=90). A total of 19,350 patients were enrolled in this paper, including 9,687 in the experiment

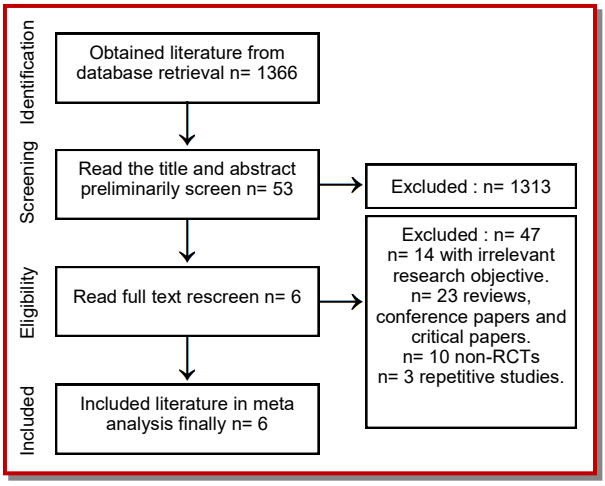

Figure 1: Flow-chart of selection process and results

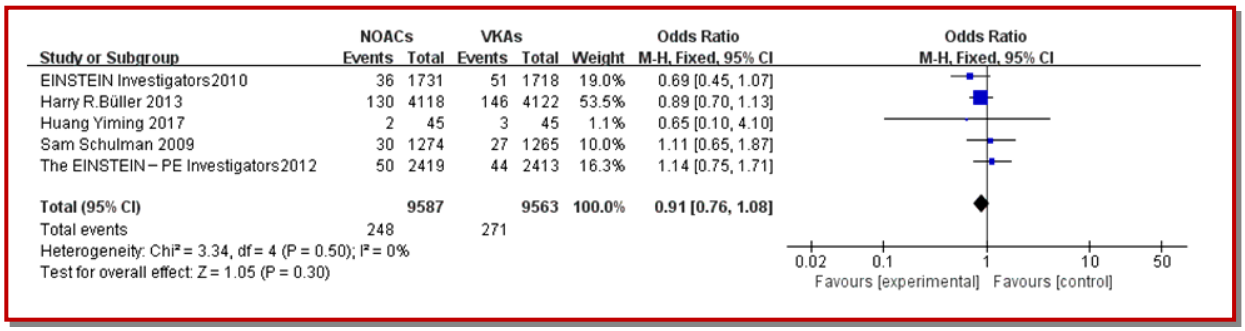

Figure 2: Forest plot of risk of recurrent venous thromboembolism (VTE) between NOACs and vitamin K antagonists

Table I

Demographic and clinical characteristics of included studies

Included studies	Sample size		Patients	Age (year)		Sex (%)		EG (NOACs)	CG (VKAs)	Follow-up time (month)
	EG	CG		EG	CG	EG	CG			
Schulman et al., 2009	1274	1265	VTE	55.0 (15.8)	54.4 (16.2)	58	58.9	Dabigatran (150 mg bid)	Warfarin (INR2.0-3.0)	6
Bauersachs, 2010	1731	1718	DVT	55.8 (16.4)	56.4 (16.3)	57.4	56.3	Rivaroxaban (15 mg bid, after 3 weeks 20 mg qd)	VKAs (INR2.0-3.0)	12
Buller et al., 2012	2419	2413	PE	57.9 (7.3)	57.5 (7.2)	54.1	51.7	Rivaroxaban (15 mg bid, after 3 weeks 20 mg qd)	VKAs (INR2.0-3.0)	12
Buller et al., 2013	4118	4122	VTE	55.7 (16.3)	55.9 (16.2)	57.3	57.2	Edoxaban (30/60 mg qd*)	Warfarin (INR2.0-3.0)	12
Huang, 2017	45	45	VTE	64.3 (4.2)	64.1 (4.0)	55.6	57.8	Rivaroxaban (15 mg qd)	Warfarin (INR2.0-3.0)	6
Sun et al., 2017	100	100	VTE	55.2 (16.8)	56.0 (16.2)	58.0	57.9	Dabigatran (150 mg bid)	Warfarin (INR2.0-3.0)	6

group and 9,663 in the control group. The basic characteristics and methodological quality evaluation results of the enrolled studies were shown in Table I.

Meta-analysis results of the enrolled studies

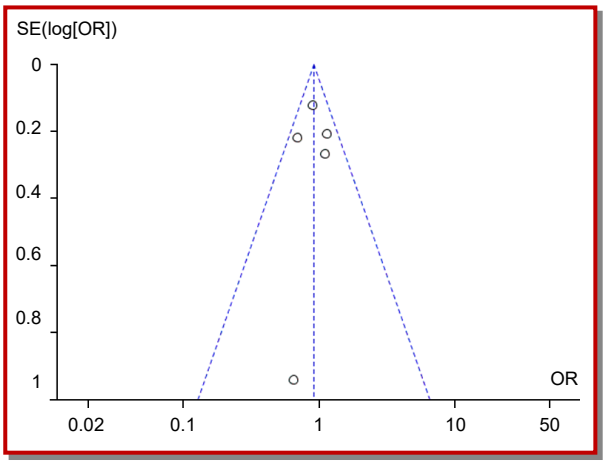

Figure 3: Funnel plot of risk of recurrent venous thromboembolism between NOACs and vitamin K antagonists

Thrombus recurrence rate

Altogether 5 of the enrolled studies had reported thrombus recurrence among the objects of study after treatment (Figure 2). The analysis results indicated no significant difference in the heterogeneity test (p=0.5, I2 =0%). The funnel plots for nine indexes were symmetric, indicating no obvious publication bias (Figure 3). Therefore, the fixed effect model was adopted for meta-analysis, the results of which indicated that the thrombus recurrence rate in VKAs group was higher than that in NOACs group after treatment, but the difference was not statistically significant (OR=0.91, 95%CI 0.76-1.08, P=0.3).

Incidence of bleeding event

Five of the enrolled studies had reported the bleeding event among the objects of study after treatment (Figure 4). The analysis results indicated no significant difference in the heterogeneity test (p=0.14, I^2 =42%). The funnel plots for nine indexes were symmetric, indicating no obvious publication bias (Figure 5). Therefore, the fixed effect model was adopted for meta-analysis,

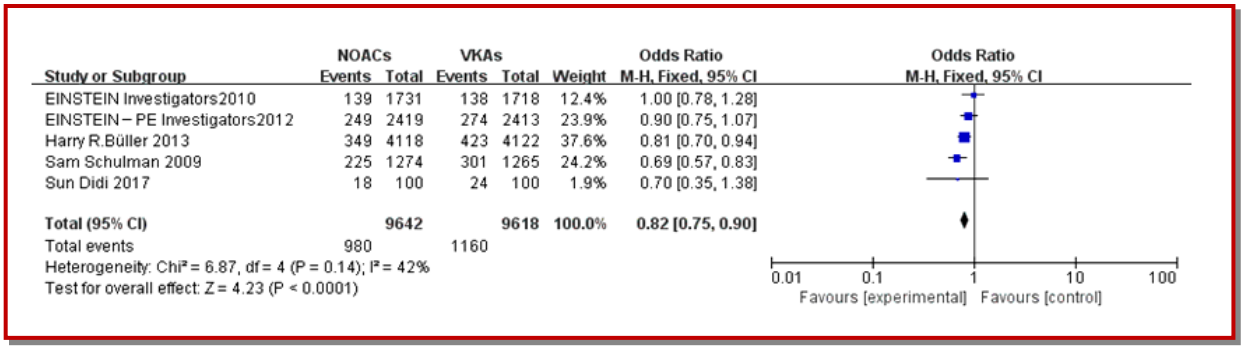

Figure 4: Forest plot of risk of bleeding event between NOACs and vitamin K antagonists

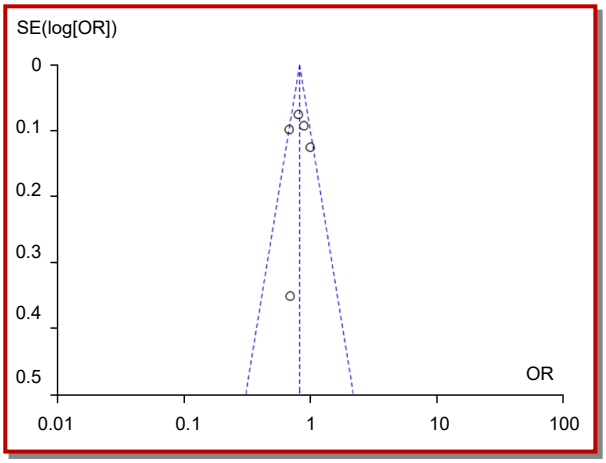

Figure 5: Funnel plot of risk of bleeding event between NOACs and vitamin K antagonists

the results of which indicated that the total bleeding rate in vitamin K antagonists group was higher than that in NOACs group after treatment, and the difference was highly statistically significant (OR=0.82, 95% CI 0.75-0.90, p<0.0001).

Discussion

This paper has systemically evaluated the effectiveness and safety of NOACs and vitamin K antagonists on treating venous thromboembolism. Our research results indicate that NOACs have comparable efficacy to vitamin K antagonists, the thrombus recurrence rate in vitamin K antagonists group after treatment is higher than that in NOACs group, but the difference is not statistically significant (p=0.3). This finding reveals that the efficacy of NOACs is not necessarily superior to that of vitamin K antagonists; however, such result may be related to the small number of literature enrolled in this paper. Typically, evidence-based medical evidence is lacking in domestic and foreign studies, and more studies are thereby required. The total bleeding rate in vitamin K antagonists group after treatment is higher than that in NOACs group, and the difference is statistically significant (p<0.0001), suggesting that NOACs display higher safety than vitamin K antagonists, which is consistent with the results of a recently published study (Castellucci et al., 2014; Dentali et al., 2015). Overall, NOACs are comparable or superior to vitamin K antagonists in terms of effectiveness and safety, indicating that NOACs may be a favorable choice for patients who can not use or can not accept warfarin treatment or can not sufficiently carry out INR monitoring (Table II).

The vitamin K antagonists warfarin is still the most prescribed oral anticoagulant drug worldwide, but several randomized controlled trials have confirmed that NOACs have a significantly lower risk of bleeding than warfarin, and that the efficacy is usually better than warfarin (Conway et al., 2017). The risk of intraocular hemorrhage between warfarin and NOACs, involving a total of 102,627 patients in 12 studies. Studies have shown that compared with warfarin, the use of NOACs can reduce the risk of intraocular hemorrhage by 22% (rr, 0.78; 95% CI, 0.61-0.99), with no significant difference in heterogeneity (I^2=4.8%, p=0.40). Patients with atrial fibrillation and venous thromboembolism have similar benefits. The results of the study are instructive for the selection of anticoagulant drugs in patients with high risk of retinal and subretinal hemorrhage, and preference should be given to NOACs during perioperative period (Sun et al., 2017). Furthermore, some investigators investigated the correlation between anticoagulants (warfarin vs NOACs) and death from intracerebral hemorrhage. The study involved 141,311 patients and results showed that NOACs or warfarin caused an increased risk of in-hospital mortality in patients with intracerebral hemorrhage. However, warfarin has a higher risk of death from cerebral hemorrhage than NOACs (Inohara et al., 2018). Besides, a study on circulation, which suggested that for old patients with atrial fibrillation at the age of ≥90, warfarin could reduce the risk of ischemic stroke and bring net clinical benefit. Compared with warfarin, NOACs contribute to reducing the risk of intracranial bleeding, revealing that NOACs are the better choice for old patients to prevent thrombus (Chao et al., 2018).

Table II

Quality evaluation of included studies

Included studies	Generation of allocation sequence	Allocation concealment	Double blinding	Withdrawal	Total
Schulman et al., 2009	√	√	√	√	7
Bauersachs et al., 2010	√	√	√	√	7
Buller et al., 2012	√	√	√	√	7
Buller et al., 2013	√	√	√	√	7
Huang, 2017	√				2
Sun et al., 2017	√			√	4

Similarly, in anticoagu-lation treatment of patients with atrial fibrillation and valvular heart disease, NOACs reduce stroke and systemic embolism, while reducing the incidence of bleeding events (Pan et al., 2017). Bleeding is the most common complication of anticoagulant therapy, and the risk of bleeding is greater in older, poor renal function, advanced cancer, and frailty patients. So, may be NOACs are a reasonable alternative to vitamin K antagonists. But, A latest study from JAMA had studied the relationship between warfarin application and cancer morbidity among the Norwegian population, and their results indicated that warfarin might have extensive anti-cancer potentials among populated aged over 50 years. This finding may be of great significance to patients requiring anticoagulant treatment in selecting the oral anticoagulants (Haaland et al., 2017). Consequently, we should better understand venous thromboembolism, as well as the management and treatment of venous thromboembolism in the elderly, cancer and after surgery, and select the suitable anticoagulant, so as to achieve the optimal therapeutic effect.

Nevertheless, this study is associated with some potential limitations. Firstly, among the enrolled literature, patients in all studies are not randomly divided according to the clinical manifestations. Therefore, the heterogeneity in baseline characteristics among different groups can not be excluded. Moreover, the doses of anticoagulants and follow-up periods are different, which may potentially lead to certain heterogeneity. Secondly, large study data among the Chinese population are lacking, and the research results may thereby be not representative. Finally, the insufficient outcome index and underlying diseases in patients enrolled in each study may affect the research results.

Conclusion

New oral anticoagulants have comparable efficacy to vitamin K antagonists, but the former can reduce the incidence of bleeding event and are superior to the latter in terms of safety. However, the conclusion in this study should be further verified through clinical studies due to the restricted number and quality of the enrolled studies.

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Conflict of Interest

Authors declare no conflict of interest

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