A New Generation of Oral Direct Anticoagulants

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Abstract—After more than 50 years of thrombosis treatment and prophylaxis being based on heparin and vitamin K antagonists, a new generation of oral, direct anticoagulants is now available. The past 5 years have brought a strikingly large number of trials that evaluated these new oral anticoagulants in a range of clinical trials, particularly nonvalvular atrial fibrillation, thrombosis prophylaxis after major joint replacement surgery, treatment of venous thromboembolic events, and, most recently, acute coronary syndrome. These studies have been notably similar in design between the drugs for specific indication. This review focuses on the 3 drugs that either have recently been approved by the US Food and Drug Administration (dabigatran and rivaroxaban) or have the most mature phase III clinical data (apixaban). (Arterioscler Thromb Vasc Biol. 2012;32:569-574.)

Key Words: deep vein thrombosis ■ pulmonary embolism ■ anticoagulation ■ acute coronary syndrome ■ atrial fibrillation ■ dabigatran ■ rivaroxaban ■ apixaban

Anticoagulation therapy has been a remarkably stable field of medicine for more than 50 years. In 1960, Barritt and Jordan published a randomized trial that demonstrated that a regimen of 6 days of intravenous heparin followed by an oral vitamin K antagonist resulted in a marked, significant reduction in fatal and nonfatal recurrent events.1 Their study even included a simple algorithm for dose adjustment of the vitamin K antagonist based on the prothrombin time. Factoring in the current approach of using of low-molecular-weight heparin, this fundamental study has remained the standard of care for more than 50 years, and it is hard to imagine any other single clinical study having as durable an impact on clinical practice and contributing to the saving of more lives.

Although warfarin and related oral vitamin K antagonists have been a mainstay of medicine for the treatment and prophylaxis of thrombosis, indeed being the only oral anticoagulants for more than 50 years, warfarin is the drug we all love to hate. As Ansell et al summarized it, “[Vitamin K antagonists] are challenging to use in clinical practice for the following reasons: (1) they have a narrow therapeutic window; (2) they exhibit considerable variability in dose response among patients due to genetic and other factors; (3) they are subject to interactions with drugs and diet; (4) their laboratory control is difficult to standardize; and (5) maintenance of a therapeutic level of anticoagulation requires a good understanding of the pharmacokinetics and pharmacodynamics of warfarin and good patient communication.”2 Therefore, there has been a concerted effort on the part of the hematology and cardiology communities and the pharmaceutical industry to develop a new generation of oral anticoagulants that may offer the same or improved efficacy and safety without the unique challenges of warfarin. We are now seeing the fruits of that labor.

New agents have been a major source of excitement; with numerous studies published in the past 5 years on the 3 leading new oral direct anticoagulants: dabigatran, rivaroxaban, and apixaban. There are also several additional promising drugs in earlier stages of clinical development. In this review, we focus on dabigatran, rivaroxaban, and apixaban and discuss the clinical trial results and the application of these agents.

Some initial words of caution. For all the difficulties with warfarin, virtually every aspect of the drug is well known, including its mechanism of action and metabolism; a universally available tool for monitoring its therapeutic level; and widely available, highly effective reversal agents.2 Vitamin K, fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa have all been well validated for warfarin reversal, depending on the urgency of the situation.2 And although warfarin certainly is associated with a serious risk of bleeding, it is quite rare for patients to develop other noncoagulation-related toxicities. For the new direct anticoagulants to be widely adapted, they will need to be not only noninferior or superior to warfarin for coagulation-related safety and efficacy, but also comparably safe regarding the other realms of possible side effects. This is best illustrated by the recent negative experience with ximelagatran, the first oral direct thrombin inhibitor that was widely studied in humans. Despite the fact that ximelagatran was noninferior to enoxaparin/warfarin for the treatment of deep venous thrombosis, a critical increase in liver function abnormalities was observed in some patents,3 resulting in its withdrawal from therapeutic development in 2006 by AstraZeneca.
New Oral Agents

Three new direct oral anticoagulants either have been recently approved by the US Food and Drug Administration (FDA) (dabigatran and rivaroxaban) or are the later stages of clinical trials (apixaban) (Figure). These are summarized in the Table. They are all small molecules and readily absorbed orally. These agents inhibit specific activated enzymes of the coagulation system, whereas warfarin and other vitamin K antagonists reduce the production of the coagulation proenzymes, and heparin or low-molecular-weight heparin require a cofactor, such as antithrombin III. Unlike heparin, the inhibitory effect does not require a cofactor, such as antithrombin III. Figure adapted from Eriksson et al.4 TF indicates tissue factor.

Development/Clinical Trials

The new oral anticoagulants have followed similar paths to development. They were studied in thrombosis prophylaxis for high-risk orthopedic patients, nonvalvular atrial fibrillation, and treatment and secondary prophylaxis for venous thromboembolic disease. More recent studies have included acute coronary syndrome (ACS), and extended thrombosis prophylaxis in medical patients. The studies were designed with fixed doses of the drug and did not incorporate therapeutic efficacy monitoring or dose titration. Most of the studies were powered for noninferiority.

Nonvalvular Atrial Fibrillation

Dabigatran was the first of the new oral anticoagulants to be approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.4 This was based on the impressive results of the RE-LY trial.5 Patients with nonvalvular atrial fibrillation and a risk for stroke were randomly assigned to 150 mg twice daily or 110 mg twice daily of dabigatran or to dose-adjusted warfarin. Both doses of dabigatran were noninferior to warfarin for the primary efficacy end point of stroke or systemic embolism and the primary safety end point of major bleeding.5,6 The higher dose of dabigatran resulted in a relative risk of stroke or systemic embolism of 0.66 compared with dose-adjusted warfarin. This was significant for superiority (P<0.001), without a significant difference in bleeding rates.5,6 The 110 mg twice daily dose of dabigatran was noninferior to warfarin for stroke or systemic embolism but significantly safer for major and all bleeding episodes. Of note, both the 150 mg and the 110 mg doses of dabigatran were associated with significantly lower rates of intracerebral and subdural hemorrhage than warfarin. In a controversial move, the FDA approved 150 mg of dabigatran twice daily for nonvalvular atrial fibrillation, as well as a lower dose of 75 mg, not the 110 mg dose, despite the fact that the 75 mg dose was not tested.7 For nonvalvular atrial fibrillation, the recommended dose of dabigatran is 150 mg twice daily. In moderate azotemia, creatinine clearance (CrCl) 15 to 30 mL/min, the recommended dose of dabigatran is 75 mg twice daily (Pradaxa product insert).
In the RE-LY study, dabigatran was associated with an increased risk in gastrointestinal bleeding. The relative risk for any kind of gastrointestinal bleeding for dabigatran at 150 mg twice daily versus warfarin was 1.50 (95% CI 1.19–1.89). This may be an inherent risk of any of the new oral, direct anticoagulants, but further investigation will be required. Questions have also been raised regarding possible increased rates of myocardial infarction with dabigatran in the RE-LY trial, with a relative risk of myocardial infarction of 1.35 (95% CI 0.98–1.87). For more severe azotemia, (CrCl <15 mL/min) or for patients who are on dialysis, dosing guidelines are unavailable, and dabigatran should not be used at this time.

Rivaroxaban was also successfully studied in nonvalvular atrial fibrillation by Patel et al in the ROCKET AF trial. Patients with nonvalvular atrial fibrillation and at least 2 additional risk factors, or a history of prior stroke, transient ischemic attack, or systemic embolization, were randomly assigned to 20 mg of rivaroxaban daily or dose-adjusted warfarin. Patients with CrCl of 30 to 49 mL/minute received 15 mg of rivaroxaban daily. Rivaroxaban resulted in a significantly reduced relative risk of the primary efficacy end point of composite of stroke and systemic embolism (hazard ratio [HR] 0.79; P=0.015). The hazard ratios of the additional efficacy end points of vascular death, stroke, and embolism and hemorrhagic stroke also were significantly better for rivaroxaban. The composite of major and nonmajor clinically relevant bleeding events was similar between rivaroxaban and warfarin, and although the numbers were small, rivaroxaban was associated with significantly lower rates of fatal bleeding and intracranial hemorrhages than warfarin. Lastly, rivaroxaban showed a slightly lower rate of myocardial infarction than warfarin (HR 0.81, 95% CI 0.63–1.06, not-significant).

Rivaroxaban has now been approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The standard dose for patients with CrCl >50 mL/min is 20 mg daily with the evening meal. For CrCl 15 to 50 mL/min., the dose is 15 mg orally once daily, and it should be avoided with CrCl <15 mL/min (Xarelto product insert).

Apixaban has also been successfully studied in patients with nonvalvular atrial fibrillation and at least 1 additional risk factor in the ARISTOTLE study. Apixaban at 5 mg twice daily was compared with dose-adjusted warfarin. The HR for stroke or systemic embolism for apixaban was 0.79 (95% CI 0.66–0.95, P=0.01), and the HR for major bleeding was 0.69 (95% CI 0.60–0.80, P<0.001). The benefit also included reduced all-cause mortality (HR 0.89, 95% CI 0.80–0.99, P=0.047). The rates of myocardial infarction and gastrointestinal bleeding showed a trend toward lower rates for apixaban, although not significant. Although it is highly promising, apixaban has not yet been FDA approved for atrial fibrillation.

Both dabigatran and rivaroxaban have achieved success for nonvalvular atrial fibrillation, demonstrating efficacy superiority, with no significant increase in bleeding, and they have now entered widespread clinical practice for these indications. In making the choice to prescribe one of the new agents or stick with warfarin, the treating physician will need to balance the potential advantages of the new agents, such as less dietary restrictions, no routine monitoring, and a significant but modest improvement with efficacy, with their limitations, such as absence of reversal agent, absence of validated monitoring test, fewer data on potential interactions with concomitant drugs and comorbidities, and less familiarity with the drugs.

**Thrombosis Prophylaxis in High-Risk Orthopedic Patients**

Deep venous thrombosis following major orthopedic surgery is a major postoperative complication, and routine prophylaxis with low-molecular-weight heparin has become the standard of care. The risk of thrombosis persists for at least a month after hospital discharge. However, the cost and inconvenience of low-molecular-weight heparin in this setting reduces compliance, particularly after hospital discharge.

A second area in which the new oral anticoagulants have begun to have an impact is for thrombosis prophylaxis in the high-risk orthopedic patients, undergoing knee or hip replacement. Different studies for all 3 drugs used enoxaparin for the control arm, which followed either the European standard of care (40 mg of enoxaparin daily, starting the evening before the surgery) or the American standard (30 mg of enoxaparin twice daily, starting 12–24 hours after the surgery).

In 4 separate trials, (RECORD 1 through 4), 10 mg of rivaroxaban once daily was compared with 40 mg of enoxaparin once daily (RECORD 1–3) or 30 mg twice daily (RECORD 4) in hip replacement (RECORD 1 and 2) and knee replacement (RECORD 3 and 4) summarized in16. A pooled analysis of the 4 studies compared the effect of rivaroxaban with enoxaparin on symptomatic venous thromboembolic event (VTE) plus all-cause mortality and bleeding events. The primary efficacy end point at day 12 occurred in 0.5% of the patients on rivaroxaban compared with 1.0% on enoxaparin (HR 0.48; 95% CI 0.30–0.76; P=0.001). There was no significant increase in the safety end point of major and nonmajor clinically relevant bleeding. The efficacy benefit of rivaroxaban was observed in all 4 RECORD studies, although not all individual studies achieved statistical significance. In July 2011, rivaroxaban was FDA approved to reduce the risk of deep vein thrombosis and pulmonary embolism following knee or hip replacement surgery. For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended. For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

Dabigatran has also been extensively studied in the high-risk orthopedic population in a series of studies, RE-NOVATE (THR), RE-MOBILIZE (TKR), and RE-MODEL (TKR). As with rivaroxaban, the control arms had different enoxaparin regimens, depending on the local standard of care. RE-MODEL and RE-NOVATE were conducted in Europe and used 40 mg daily, whereas RE-MOBILIZE was conducted in the US and used 30 mg of enoxaparin twice daily. Dabigatran was tested at both 150 and 220 mg once daily in all 3 studies.

For the composite of total VTE and all-cause mortality during treatment, 150 and 220 mg of dabigatran daily was
noninferior to 40 mg of enoxaparin daily, in the RE-NOVATE and RE-MODEL trials with similar bleeding rates. Interestingly, in the RE-MOBILIZE trial, both doses of dabigatran resulted in higher rates of the composite thrombosis/all-cause mortality, compared with enoxaparin, and failed to demonstrate noninferiority. This failure in the RE-MOBILIZE trial may be due to a number of possible considerations, but the difference in enoxaparin regimen is 1 intriguing possibility. Dabigatran was noninferior to 40 mg of enoxaparin once daily, but inferior to 30 mg twice daily. In all 3 trials, there were no significant differences in bleeding rates. At present, dabigatran has not been FDA approved for thrombosis prophylaxis in the high-risk orthopedic population.

Apixaban has been evaluated in high-risk orthopedic patients in the ADVANCE trials. In the first, apixaban (2.5 mg twice daily) was compared with 30 mg of enoxaparin twice daily for the prevention of VTE after total knee replacement. The primary efficacy rates were low and similar (apixaban, 9.0%; enoxaparin, 8.8%) but the statistical end point of noninferiority was not met (P=0.06). However, the composite of major and clinically relevant nonmajor bleeding was significantly lower with apixaban than with enoxaparin (2.9% versus 4.3%; P=0.03).

In the subsequent ADVANCE-2 (TKR) studies, apixaban was compared with 40 mg of enoxaparin once daily, starting 12 hours before surgery. The primary outcome was the composite of asymptomatic and symptomatic deep vein thrombosis, nonfatal pulmonary embolism, and all-cause death during treatment. In ADVANCE-2, the primary outcome was observed in 15% of apixaban-treated and 24% of enoxaparin-treated patients (relative risk 0.62; 95% CI 0.51–0.74; P<0.0001; absolute risk reduction 9.3%). Major or clinically relevant nonmajor bleeding occurred in 4% in the apixaban arm 5% with enoxaparin (not significant).

In the ADVANCE-3 trial the primary efficacy outcome occurred in 1.4% in the apixaban group and 3.9% of the enoxaparin group (relative risk 0.36; P<0.001 for both noninferiority and superiority). The composite outcome of major and clinically relevant nonmajor bleeding was also not significantly different between the 2 treatments. Interestingly, as with dabigatran, apixaban achieved noninferiority status when compared with 40 mg of enoxaparin daily but not when compared with 30 mg of enoxaparin twice daily.

An oral anticoagulant that is noninferior for safety and efficacy to enoxaparin for thrombosis prophylaxis in joint replacement patients would be very gratifying because of greater patient comfort and presumed compliance. This has now been achieved with rivaroxaban. Few would argue that the greater convenience and comfort of an oral agent compared with subcutaneous injections of enoxaparin would make “noninferior” highly attractive. Furthermore, rivaroxaban is priced substantially lower than generic enoxaparin. So in this case, improved efficacy, safety, and patient comfort comes with a reduced price. It has yet to be determined whether dabigatran or apixaban will ultimately join rivaroxaban for the indication of thrombosis prophylaxis after major joint replacement surgery.

**Thrombosis Prophylaxis in High-Risk Medical Patients**

Although the high-risk medical patient population tends to have lower thrombosis rates than surgical patients, the rate of thrombosis remains sufficiently high that routine pharmacological prophylaxis is widely used. Enoxaparin prophylaxis has been shown to significantly reduce the rate of thrombosis and is now standard of care. The MAGELLAN trial evaluated rivaroxaban for thrombosis prophylaxis in high-risk medical patients. In the first part of the study, 10 mg of rivaroxaban daily was compared with 40 mg of enoxaparin daily in acutely ill medical patients at high risk for thrombosis. At day 10, the rates of thrombosis were the same, at 2.7%. However, the bleeding rate was higher with rivaroxaban than enoxaparin (2.8% versus 1.2%). The full study has yet to be published. At this time, it is premature to conclude that 1 or more of the new oral anticoagulants will provide comparable efficacy and safety as enoxaparin or other low-molecular-weight heparins for thrombosis prophylaxis in the high-risk medical patients. More studies will be required.

**Treatment of Venous Thrombosis**

One key area of interest for the new anticoagulants is for VTE treatment. In the EINSTEIN trial, patients with VTE were randomly assigned to 15 mg of rivaroxaban BID for 3 weeks followed by 20 mg once daily or 1 mg/kg enoxaparin twice daily (for at least 5 days), followed by warfarin or acenocoumarol, started within 48 hours after randomization. The study was designed to evaluate rivaroxaban as the initial and sole anticoagulant, but to facilitate enrollment, patients were allowed up to 48 hours of IV heparin, low-molecular-weight heparin, or fondaparinux before enrollment. The intended duration of treatment was based on the patient’s individual circumstance and was typically 3, 6, or 12 months. The primary efficacy outcome was symptomatic, recurrent venous thromboembolism (composite of deep vein thrombosis or nonfatal or fatal pulmonary embolism). The principal safety outcome was the composite of major or clinically relevant nonmajor bleeding. Rivaroxaban showed a trend toward a reduced rate of recurrent VTE (2.1%) compared with enoxaparin–vitamin K antagonist (3.0%), for an HR of 0.68 (95% CI 0.44–1.04). However, this was only significant for noninferiority (P<0.001). The rates of major or clinically relevant nonmajor bleeding were the same (8.1%).

The investigators added a continued treatment study for patients who had been treated for 6 or 12 months with a vitamin K antagonist or rivaroxaban. They were randomly assigned to receive continued with rivaroxaban or placebo. The extension study was designed to determine whether there was added benefit from longer than standard anticoagulation. As would be predicted, continued rivaroxaban therapy was associated with a reduced rate of recurrent thrombosis (1.3%) compared with placebo (7.1%) (P<0.001), but at a price of more major or clinically relevant nonmajor bleeding (rivaroxaban, 6.0%; placebo, 1.2%; P<0.001).

Dabigatran was compared with warfarin in the treatment of acute venous thromboembolism in the RECOVER study.
This study design differed from the EINSTEIN study in that all patients received an “approved parenteral anticoagulant (generally unfractionated heparin administered intravenously or low-molecular-weight heparin administered subcutaneously)” for at least 5 days before receiving either warfarin or dabigatran. Patients received 150 mg of dabigatran twice daily or INR-titrated warfarin for 6 months. The primary outcome of recurrent symptomatic, objectively confirmed venous thromboembolism and related deaths was not significantly different (dabigatran 2.4%, warfarin 2.1%; \( P<0.001 \) for noninferiority). Although major bleeding was not significantly different between dabigatran and warfarin, the HR for any bleeding favored dabigatran (HR 0.71; 95% CI 0.59–0.85; \( P<0.001 \)).

Apixaban for VTE treatment has been studied in the Botticelli dose-ranging study. Patients with symptomatic VTE were randomly assigned to receive 5 mg of apixaban twice daily, 10 mg twice daily, or 20 mg once daily or low-molecular-weight heparin followed by a vitamin K antagonist for 3 months. Interestingly, the primary efficacy end point of composite of symptomatic recurrent VTE and clinical deterioration and the safety end point of major and clinically relevant nonmajor bleeding were not significantly different between the apixaban cohorts, and there was no apixaban dose-response relationship for either end point. A larger phase III trial of apixaban for VTE treatment has not been performed.

**Acute Coronary Syndrome**

The new generation of oral anticoagulants have recently been evaluated in ACS. The essence of these studies was to determine whether addition of the anticoagulant to standard antiplatelet agents would improve cardiovascular events and overall survival, at an acceptable increase in bleeding rates.

In the recently published ATLAS study, Mega et al evaluated the addition of rivaroxaban at 2.5 or 5 mg twice daily, or placebo, to standard antiplatelet therapy for patients with ACS. All patients received low-dose aspirin, and 93% also received a thienopyridine. Both doses or rivaroxaban, as well as the pooled population on rivaroxaban, had lower rates of the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as well as lower rate of death from all causes. When results of both doses of rivaroxaban were pooled, the primary efficacy end point occurred in 8.9% of patients, compared with 10.7% in the placebo group (HR 0.84; 95% CI 0.02–0.97; \( P=0.007 \)), which represents a 1.8% absolute benefit. As would be expected, this clinical benefit was at the cost of increased hemorrhage. Rivaroxaban increased the rates of major bleeding not related to coronary artery surgery (2.1% versus 0.6%, \( P<0.001 \)) for an absolute increase of 1.5%. Rivaroxaban also increased rates of intracranial hemorrhage compared with placebo (0.6% versus 0.2%, \( P=0.009 \)).

Apixaban was similarly studied in ACS in the APPRAISE-2 trial. In this randomized trial, 5 mg of apixaban twice daily was compared with placebo, in addition to standard antiplatelet therapy, in patients with a recent ACS and at least 2 additional risk factors for recurrent ischemic events. The trial was terminated prematurely because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. Although there was a modest trend toward reduced primary efficacy outcomes of cardiovascular death, myocardial infarction, or ischemic stroke with apixaban versus placebo (7.5% versus 7.9%), this was not significant. In contrast, major bleeding occurred in 1.3% of apixaban treated patients compared with 0.5% of placebo, which was significant (\( P=0.001 \)). Also, a greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.

In comparing the study designs of the ACS studies, ATLAS (rivaroxaban) and APPRAISE-2 (apixaban), 1 notable difference is the relative doses of the 2 drugs. Rivaroxaban was tested at relatively lower doses when compared with apixaban. The rivaroxaban dose for ACS was 2.5 or 5 mg twice daily, compared with the initial VTE treatment dose of 15 mg twice daily or 20 mg daily for atrial fibrillation. In contrast, apixaban was tested at the same dose as that studied for atrial fibrillation (5 mg BID). This difference in relative dosing may have contributed to the greater burden of hemorrhagic complications in the apixaban study for ACS, compared with rivaroxaban, resulting in premature termination of the apixaban study.

**Conclusions and Comments**

The new oral anticoagulants represent the culmination of decades of preclinical and clinical trial development. The studies have been very large, typically involving many thousands of patients, and represent a very large investment in human capital on the part of the willing patient participants as well as the medical staff conducting the studies. Similarly, the pharmaceutical companies have invested greatly of their research and development budgets to bring these drugs through phase III trials and now approval by the FDA and foreign regulatory bodies.

But there remain a number of key limitations and unanswered questions. The similarity in study design across the different drugs and indications is notable. Dose adjustment based on weight was not incorporated into the studies. Patients with relevant comorbidities, such as thrombocytopenia, recent gastrointestinal bleeding, liver dysfunction, and other considerations that could increase bleeding were often excluded. These exclusions from the clinical trials may therefore limit the potential application of the new direct oral anticoagulants to some subpopulations. In the real world, one still needs to treat patients with confounding issues, and selectively using enoxaparin and warfarin in those higher risk patients is not an acceptable alternative.

Monitoring and dose adjustment for the new oral anticoagulants will ultimately need to be incorporated into future practice. The current state of affairs is reminiscent of the early development of enoxaparin and other low-molecular-weight heparins. The development of the anti-factor Xa assay has been of great benefit, providing reassurance that the dose is appropriate in subsets of patients with underlying azotemia or other comorbidities. Efforts are beginning to develop and validate monitoring assays, but these assays are still not in hand. One can imagine an added burden if each of the new agents requires different technologies for monitoring.
Perhaps the greatest current limitation for the new agents is the absence of a reversal agent. No anticoagulant will ever be so safe that bleeding complications will not occur, either spontaneously, or from trauma. And for all of the limitations of warfarin, the knowledge of how to effectively reverse its affect with plasma, vitamin K, prothrombin complex concentrate, or recombinant factor VIIa and to confirm that the warfarin effect has been reversed with a INR is very reassuring. Perhaps an apt analogy is that warfarin is like our old car. It is prone to breakdowns, but when it does break down we usually know the problem, and our neighborhood service station knows how to fix it and has the parts. The new agents are analogous to the new sports car of our dreams. However, before we start off down the highway, it is best to make sure we know where the emergency brake is—and let’s hope we continue to smile when we look in the rearview mirror.

Disclosures

None.

References

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