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Extended Anticoagulation Therapy for the Primary and Secondary Prevention of Venous Thromboembolism

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Abstract

Extending the period of anticoagulation is an active area of investigation in both primary and secondary prevention of venous thromboembolic disease. In orthopaedic surgery, particularly in patients undergoing hip surgery, there is a growing interest in using extended anticoagulation beyond that traditionally given in the postoperative period using low-molecular weight heparin, oral anticoagulants, or newer agents such as fondaparinux sodium. Most studies show a benefit to extending anticoagulation without a considerable increase in major bleeding. There have been several large clinical trials addressing the question of extending oral anticoagulation in secondary prevention of venous thromboembolism (VTE). Just how long anticoagulation should be given in the treatment of venous thromboembolic disease remains an open question, depending on the nature of the initial VTE, associated patient risk factors and the risks of major bleeding. Future directions include the use of newer agents for anticoagulation as well as methods of better defining who will benefit most from extended anticoagulation based on an identification of risk factors with the aid of markers such as D-dimer or residual vein thrombosis.

Oral anticoagulants have a proven benefit for the primary and secondary prevention of venous thromboembolism (VTE), but optimal therapy requires a careful assessment of the benefits and risks of anticoagulation when deciding to treat a patient. Primary prevention refers to preventing a first time event – in this case an episode of thrombosis – in patients or a population who have never had an episode of thrombosis, while secondary prevention refers to preventing a recurrent thrombosis in patients or a population who have already been diagnosed with venous thromboembolic disease. For VTE, the risks are dynamic: the risk of thromboembolism is high in the months immediately following the diagnosis but may diminish with time. Most experts quote a lifetime recurrence rate for idiopathic VTE of about 30% based on the study by Prandoni et al.,[1] which noted a cumulative recurrence rate of 30.3% after 8 years of follow-up. The challenge then becomes balancing the risk of recurrence versus the risk of major bleeding and determining how long anticoagulation therapy should continue. The value of prolonged anticoagulation is an area of active investigation, especially for conditions such as secondary prophylaxis of VTE and primary prophylaxis of VTE following orthopaedic surgery. These conditions are also fertile areas for the study of the effectiveness of new anticoagulants.

This review provides an overview of extended anticoagulation, particularly as it pertains to areas

where there are ongoing studies and controversies. This includes evidence that extending anticoagulation in the postoperative setting following orthopaedic procedures may be of some benefit. Historical and more recent data regarding extending anticoagulation in the setting of venous thromboembolic disease in an effort to decrease recurrence of thrombosis are also discussed.

1. Primary Prophylaxis in Orthopaedic Surgery

Orthopaedic surgery incurs a significant risk of VTE. Estimates of venogram-documented deep vein thrombosis (DVT) 7–14 days after hip surgery (fracture or replacement) or knee replacement surgery are 50–60% in patients without prophylaxis. Estimates of objectively documented pulmonary embolism (PE) following hip or knee replacement surgery are 7–11% in patients without prophylaxis.[2] Previously, guidelines have recommended prophylactic anticoagulation with either low-molecular weight heparin (LMWH) or an oral anticoagulant such as warfarin for 7–10 days following total hip arthroplasty or total knee arthroplasty.[2] Newer evidence has shown a benefit from extending anticoagulation in the case of hip fracture repair or elective hip replacement, and the most recently released guidelines[3] now recommend extended anticoagulation in those settings. Newer anticoagulants such as fondaparinux sodium or ximelagatran are also very effective for prophylaxis.

Most studies addressing these questions are randomised controlled trials using objectively documented endpoints for the diagnosis of VTE. Documented symptomatic episodes are also included but most episodes are asymptomatic. In a recent meta-analysis, Douketis et al.[4] compared symptomatic outcomes with outcomes based on venography in patients undergoing elective knee or hip replacement following 7–10 days of prophylaxis with either LMWH or warfarin. Symptomatic VTE events occurred in 1.1% of patients undergoing any orthopaedic procedure in the 7–10 days following surgery compared with a 16% rate of VTE detected by venography at day 7–10 in patients following hip surgery and 38% in patients undergoing knee surgery. The frequency of symptomatic, but nonfatal, VTE was 3.2% at 3 months after hip or knee replacement, while the incidence of fatal PE was 0.1%. Hip surgery was found to have a higher rate of symptomatic events compared with knee replacement (2.5% vs 1.4%). It is controversial as to how significant asymptomatic thrombi are, but it is currently not possible to identify which patients will have thrombi that will become clinically significant or even fatal.

Knowing when a patient undergoing orthopaedic surgery is at greatest risk for thromboembolism can help determine the length of time that prophylaxis will be beneficial. On the basis of discharge data from the state of California, USA, the median time to an episode of symptomatic DVT is 17 days after hip surgery, in contrast with knee surgery, where the median time is 7 days.[5] Therefore, anticoagulation given only in hospital may be inadequate, and there are a number of studies investigating extended postoperative regimens. Extending warfarin therapy for an additional 4 weeks in patients undergoing elective hip repair decreased the incidence of VTE by approximately 5% compared with placebo (0.5% vs 5.1%; 95% CI 1.15%, 7.99%) in a study of 360 patients by Prandoni et al.[6] This only included patients who developed thrombosis after hospital discharge, as patients were screened with compression ultrasonography of the proximal-vein system prior to hospital discharge and had to be free of thrombosis as a criterion for inclusion into the study. There was one case of major bleeding in the extended prophylaxis arm in a patient with a supra-therapeutic international normalised ratio (INR) and none in the control group.

Many recent studies have focused on using LMWH rather than warfarin in extended prophylaxis following orthopaedic surgery. Using postoperative LMWH for approximately 30 days has been shown to significantly reduce the incidence of objectively documented DVT in patients who have had hip arthroplasty, although the benefit is less certain for patients who have had knee operations.[7] A recent meta-analysis[5] of six studies compared

LMWH with placebo for 18–28 days after discharge. All studies were randomised, double-blinded, measured events by venography, and included patients who were undergoing hip replacement. All results favoured the use of LMWH versus placebo which, when combined, showed a relative risk reduction (RRR) of 41% for VTE. Another meta-analysis including these six studies plus additional three studies found similar results: an overall reduction in the number of VTE events, with a more significant benefit in patients undergoing elective hip repair than in patients undergoing elective knee repair.[8] In patients undergoing hip repair, there was a 1.4% incidence of VTE in those receiving LMWH after hospital discharge compared with 4.3% in patients receiving placebo. In patients undergoing knee replacement, there was an incidence of VTE in 1.4% of patients receiving LMWH after hospital discharge compared with 1% of patients receiving placebo, but this was based on only a small number of patients and an even smaller number of actual events. The total duration of prophylaxis in these studies ranged from 27 to 42 days. When a vitamin K antagonist and LMWH were compared directly in the setting of extended prophylaxis after elective hip replacement, efficacy was similar, while patients on the vitamin K antagonist experienced greater bleeding.[9] This study included more than a thousand patients who were prospectively randomised to the LMWH reviparin sodium or the oral anticoagulant acenocoumarol on postoperative day 3 extending to 6 weeks after surgery. Thromboembolic events occurred in 2.3% of patients assigned to LMWH compared with 3.3% of those receiving acenocoumarol (95% CI –0.8%, 2.8%; $p = 0.3$). Acenocoumarol, however, was associated with an increase in bleeding complications, with a rate of 5.5% compared with 1.4% in those receiving LMWH ($p = 0.01$).

One of the newer anticoagulants, fondaparinux sodium has been studied in the setting of acute and extended orthopaedic prophylaxis. The development of fondaparinux sodium, a synthetically derived pentasaccharide that binds to and activates antithrombin, is a further refinement on the mechanism of action of heparin.[10] Because fondaparinux sodium lacks the longer saccharide chains required for binding to thrombin compared with heparin or even LMWH, it has no effect on thrombin and is a specific, indirect inhibitor of activated factor X via its activation of antithrombin. Fondaparinux sodium is almost 100% bioavailable, with little protein binding. It has a predictable antithrombotic effect and requires no coagulation monitoring. Fondaparinux sodium has good absorption from subcutaneous depots, reaches peak concentrations in 1–3 hours, and has an effective half-life of 17 hours. Fondaparinux sodium does not induce heparin/platelet factor 4 antibodies or cause heparin-induced thrombocytopenia. It is excreted entirely by the kidneys and is not recommended in patients with renal impairment (creatinine clearance of <30 mL/min).[10]

Fondaparinux sodium, which has been shown to be as good as, and potentially better than, enoxaparin prophylaxis in the immediate postoperative period after elective hip or knee surgery[11-13] and hip fracture repair,[14] has also been studied in extended prophylaxis. When compared with placebo, fondaparinux sodium given through postoperative days 25–30 reduced the rate of venogram-documented VTE from 35% in patients who received placebo to 1.4% in patients who received fondaparinux sodium (RRR 95.9%; 95% CI 87.2%, 99.7%; $p < 0.001$).[15] Symptomatic VTE was also reduced from 2.7% to 0.3% (RRR 88.8%; $p = 0.02$). Although not statistically significant, there was a trend towards more bleeding in the group that received fondaparinux sodium ($p = 0.06$). Fondaparinux sodium has not yet been compared directly with LMWH for extended prophylaxis.

Reflecting these data, the newest guidelines for thrombotic prophylaxis[3] have included grade 1A recommendations to use anticoagulants after elective hip replacement or fracture repair for 28–35 days, while recommending only 10 days of anticoagulation following knee replacement surgery. Agents recommended include fondaparinux sodium, LMWH and oral vitamin K antagonists, all grade 1A recommendations for the 10 days following surgery. LMWH and oral vitamin K antagonists are also grade 1A recommendations for use in extended pro-

phylaxis for up to 28–35 days, while fondaparinux sodium is a grade 1C+ recommendation for use in extended prophylaxis (grade 1C refers to data that come from either observational studies or from randomised clinical trials that use a group that is comparable, but not exactly the same, while the '+' rating implies particularly persuasive evidence). The use of extended prophylaxis in either hip fracture surgery or elective hip replacement should now be standard, while the use of anticoagulation in total knee replacement surgery should be limited to the 10 days following surgery unless special circumstances indicate the need for more prolonged therapy (e.g. immobility or prolonged bed rest). The use of fondaparinux sodium, LMWH or a vitamin K antagonist is a reasonable choice, depending on physician and institutional familiarity with the individual agent.

2. Secondary Prophylaxis in Venous Thromboembolic Disease

Treating venous thromboembolic disease involves treating the acute thrombosis for a specific period of time in order to prevent a recurrent thrombotic event. The optimal duration of treatment for venous thromboembolic disease remains controversial, and depends strongly on the initiating event, whether the event is transient or ongoing, and other underlying thrombophilic conditions. The duration of anticoagulation has gradually increased as more data suggest that longer term warfarin therapy gives added benefit of preventing recurrent VTE. With longer anticoagulation, however, comes a longer exposure to the risk of bleeding, and the optimal balance of the competing risks remains in a state of flux. A recent meta-analysis by Linkins et al.[16] better defined the risk of bleeding in patients who had received anticoagulation therapy. In the meta-analysis of the pooled data encompassing randomised and prospective cohort studies of more than 4000 patients treated for VTE with a target INR of 2–3, the incidence of major bleeding was 7.22 per 100 patient-years and the incidence of fatal bleeding was 1.31. Intracranial bleeds were the most dangerous, comprising 8.7% of the major bleeding episodes with 45% of them fatal. The first 3 months of anticoagulation were the most dangerous, with 2.06% major bleeding events in the first 3 months compared with 2.74% in the remaining 9 months of the year. This difference might be expected given that the initial phase of anticoagulation tends to be the most unstable period and those patients who have a propensity to bleed will declare themselves during the beginning of anticoagulation. On the basis of the data used in the meta-analysis, the researchers concluded that the risk of fatal thromboembolism with less than 6 months of anticoagulation is 0.35% per year compared with the risk of death from major bleeding of 0.18% per year. If a patient has a greater risk of major bleeding, especially if it approaches 0.35% per year, it would clearly change the benefit-risk analysis.[16]

Prandoni et al.[1] followed up a group of 355 patients after a first episode of symptomatic DVT and found that approximately one-third of patients had a recurrent thrombosis during 8 years of follow-up. Cancer or the presence of a hypercoagulable marker (which included antithrombin, protein C or S deficiencies, and lupus-like anticoagulant) were associated with a higher risk of recurrence, with hazard ratios (HRs) for recurrence of 1.72 (95% CI 131, 2.25) for cancer and 1.44 (95% CI 1.02, 2.01) for a hypercoagulable marker. Lower HRs were observed when DVTs were associated with recent surgery or trauma including fracture: 0.36 (95% CI 0.21, 0.62) for recent surgery and 0.51 (95% CI 0.32, 0.87) for trauma or fracture. Other investigators have validated these data.[17,18]

Until recently, the approach to the duration of treatment for DVT or PE was not well defined and recommendations were to treat for 1–6 months – a broad range that invited further study. Pinede et al.[19] compared 6 weeks of oral anticoagulation with 12 weeks in patients with an isolated DVT of the calf. Isolated calf DVT had a lower risk of recurrence regardless of the duration of treatment than DVT involving the proximal deep veins or PE (2.5% vs 8.2%). In a subgroup analysis, 12 weeks of anticoagulation was equivalent to 6 weeks of anticoagulation in patients with an isolated calf DVT, with

recurrence rates of 3.4% and 2.0%, respectively after 1 year following the cessation of anticoagulation ($p = 0.58$). In patients with a proximal DVT, however, there was no statistical difference between recurrence rates in those treated for 3 and 6 months (8.1% and 8.7%, respectively), but a subgroup analysis found that patients with an idiopathic VTE, permanent risk factors or cancer had a higher risk of recurrence when compared with patients with transient risk factors. These results show the relative low risk of isolated calf DVTs compared with proximal thrombosis and provides initial data that patients with more permanent risk factors have a higher risk of recurrence.

The British Thoracic Society compared oral anticoagulation for 4 weeks with 3 months in patients with a first episode of symptomatic DVT or PE.[20] There was a significantly lower risk of recurrence in the group treated for 3 months (7.8% vs 4%, $p = 0.04$). *Post hoc* analysis demonstrated that patients who developed VTE in the postoperative setting had a very low risk of recurrence and may not need extended anticoagulation. Levine et al.[21] compared warfarin therapy for 4 weeks with 3 months in patients with venographically proven proximal DVTs. Patients with an idiopathic DVT, cancer or history of previous DVT were classified as having a continuous risk, while patients who developed DVT in the postoperative setting were considered to have a transient risk. In the first 8 weeks of follow-up after discontinuing anticoagulants, 8.6% of patients in the 4-week treatment group had a VTE event compared with 0.9% in the group continuing warfarin for an additional 8 weeks ($p = 0.009$). At 12 months, 11.5% of patients in the 4-week treatment group and 6.8% in the 12-week group had recurrent events ($p = 0.3$). A continuing risk factor was found to be a convincing predictor of recurrent events.

The DURAC (Duration of Anticoagulation) I trial[22] investigated 897 patients with an objectively confirmed first episode of DVT and randomised them to 6 weeks or 6 months of oral anticoagulation. Patients assigned to 6 weeks of treatment had an 18.1% (95% CI 14.5%, 21.6%) incidence of recurrent VTE compared with 9.5% (95% CI 6.8%, 12.2%) in the patients treated for 6 months, after 24 months of follow-up ($p < 0.001$). The highest incidence was during the first 6 months. After 6 months, the recurrences in both groups increased at about the same rate, but the overall number of events remained higher in the shorter treatment group because of the substantial number of patients who had recurred early. In the DURAC trial, it was also demonstrated that the risk of recurrence was influenced by the nature of the presenting VTE (higher risk associated with a lupus anticoagulant or anticardiolipin antibodies).

Two large studies suggested that 3 months of treatment was too short, compared with 1 year of anticoagulation, but the latter was associated with a small increased risk of major bleeding. Kearon et al.[23] compared 3 months of anticoagulation with 1 year in patients with a first episode of idiopathic VTE (proximal DVT or PE only). The study was terminated early because of a significantly increased recurrence rate in the group assigned to 3 months of therapy compared with patients who were assigned to 1 year of therapy (27.4% per patient-year vs 1.3% per patient-year). Major bleeding was also increased in the group assigned to prolonged therapy: three patients in the group receiving warfarin for 1 year compared with no events in the group taking warfarin for 3 months. Although the actual number of patients was small, there was no increase in risk of recurrence in patients who had factor V Leiden or the prothrombin gene mutation, while testing positive for markers of the antiphospholipid antibody syndrome did seem to predict higher recurrence. The WODIT (Warfarin Optimal Duration Italian Trial)[24] investigators assigned patients with their first episode of idiopathic proximal DVT to either 3 months or 12 months of warfarin therapy and followed up both groups for over 37 months from randomisation, compared with only 10 months of follow-up in the Kearon trial.[23] Approximately 15% of patients in each group had a recurrence, with an average time to recurrence of 11.2 months in the group assigned to 3 months of therapy compared with 16 months in the group receiving extended warfarin. Although anticoagulation is very good at

Table I. Incidence of recurrent venous thromboembolism (VTE), duration of treatment and follow-up[a]

Study	Treatment duration (% recurrences)			Follow-up
	short (1–1.5 months)	usual (3–6 months)	long (12 months)	
British Thoracic Society[20]	9	5		1 year
Levine et al.[21]	15	9		11 months
Schulman et al.[22]	25	12		2 years
Kearon et al.[23]		20	1	10 months
Agnelli et al.[24]		16	16	3 years

a The studies by Agnelli et al.[24] and Kearon et al.[23] excluded patients who had transient risk factors for VTE, while the remaining studies included them.

preventing recurrence of VTE, it is only protective while it is being taken; when anticoagulation is stopped, the risk of recurrence rises, but this is not evident unless the duration of follow-up is sufficiently long. Table I summarises treatment duration and outcomes and shows that the incidence of recurrent VTE decreases with longer duration of treatment, but that such data are dependent on length of follow-up. Short duration of anticoagulation (1–1.5 months) is not adequate in patients with idiopathic VTE or with continuous risk factors and all three major studies showed a decreased incidence with 3–6 months of anticoagulation. Patients are protected from recurrent VTE mainly while they are on an anticoagulant, but will again have an increased risk of recurrence once they stop treatment. The study by Agnelli et al.[24] exemplifies this phenomenon: with extended follow-up, patients off anticoagulation will eventually have a risk of thrombosis that approaches that of shorter duration treatment, and after 2 years of follow-up the incidence of recurrence is about the same.

More recently, in an attempt to address the long-term high incidence of recurrent VTE and balance the risk of recurrence versus the risk of bleeding, the use of long-term lower intensity warfarin was tried. Ridker et al.[25] in the PREVENT (Prevention of Recurrent Venous Thromboembolism) trial found that using warfarin therapy titrated to an INR of 1.5–2.0 initiated after 6 months of standard warfarin therapy reduced the risk of recurrent VTE by 64% when compared with placebo (2.6 per patient-years versus 7.2 per patient-years; HR 0.36; 95% CI 0.19, 0.67; $p < 0.001$). There was no significant difference in rates of major bleeding, with 0.9 events per 100 patient-years in the treatment group and 0.4 events per 100 patient-years in the placebo group ($p = 0.25$). A subsequent study by Kearon et al.[26] compared low intensity warfarin (INR of 1.5–1.9) with conventional dose warfarin (INR 2–3) and found that conventional dose warfarin was better at preventing recurrence than low intensity warfarin (0.7% vs 0.9%; HR 2.8, 95% CI 1.1, 7.0). There was no difference in the rates of major bleeding between the two arms (0.4% and 0.9%, respectively).

Intuitively, individuals with an inherited thrombophilia (including conditions such as protein C or S deficiency, factor V Leiden and antithrombin deficiency) or acquired thrombophilia (such as the antiphospholipid antibody syndrome) should be treated more aggressively, but the precise risk of recurrence and duration of anticoagulation has not been well established by clinical trials. It is difficult to design such a trial, and the actual numbers of such patients are small. In one prospective cohort study, patients with deficiencies of antithrombin, protein C, protein S or a lupus anticoagulant[1] had an increased risk of recurrent events with an HR of 1.44 (compared with surgery which had an HR of 0.36). Of those with identified markers of thrombophilia, about one-third had lupus-like anticoagulants. Patients who have antiphospholipid antibody syndrome and have had an episode of thrombosis should be anticoagulated for life because the risk of recurrence is significantly high. In one study of inherited thrombophilias,[27] using genealogical data to determine lifetime risk of recurrent clots, protein C, protein S and antithrombin deficiency were found to be associated with risk ratios of recurrence of thrombosis on the order of 7.3 (95% CI 2.9, 18.4) for

protein C, 8.5 (95% CI 3.5, 20.8) for protein S and 8.1 (95% CI 3.4, 19.6) for antithrombin deficiency, and it is recommended that patients with one of these deficiencies and a history of thrombosis receive anticoagulants indefinitely. Factor V Leiden had less of an association with recurrent events, with a risk ratio of 2.2 (95% CI 1.1, 4.7), and a tendency toward less serious thrombotic events such as superficial thromboses. Thus, the recommendation for patients with factor V Leiden who have had an episode of thrombosis should be tailored to the individual patient after a discussion of the benefits and risks of anticoagulation as well as a discussion of specific risk factors to avoid.

3. Ximelagatran

Ximelagatran is a new anticoagulant that has been studied in the context of extended anticoagulation for secondary prevention of venous thromboembolic disease, as well as other indications. It is an oral direct thrombin inhibitor that blocks the active site of thrombin, and is a prodrug of the active anticoagulant, melagatran. Ximelagatran is rapidly absorbed after an oral dose, and is promptly metabolised to melagatran which then has a half-life of approximately 4–5 hours, but achieves effective anticoagulant levels for up to 12 hours so that twice daily dose administration is effective. Ximelagatran is not metabolised by the hepatic cytochrome P450 enzymes, has minimal if any drug-drug interactions, has a predictable effect and does not require monitoring. It is cleared by the kidney.[28]

Ximelagatran has been studied for the extended treatment of VTE. The THRIVE (THRombin Inhibitor in Venous ThromboEmbolism) III investigators[29] enrolled 1233 patients who received standard anticoagulation for treatment of an acute DVT for 6 months and were then randomised to ximelagatran 24mg twice daily or to placebo for the next 18 months. Patients assigned to ximelagatran had significantly fewer recurrent, symptomatic VTE events compared with placebo (2.8% vs 12.6%; HR 0.16; 95% CI 0.09, 0.30; $p < 0.001$). There was no significant difference in major bleeding between the two groups. An increase in alanine aminotransferase (>3 times upper limit of normal) did occur in 6% of patients in the ximelagatran arm during the first 6 months of therapy, which returned to normal whether the drug was continued or discontinued. Table II compares results of treatment with ximelagatran, low intensity warfarin and full intensity warfarin.

There continues to be debate on the appropriate duration and intensity of therapy following an idiopathic episode of thromboembolism.[30-32] The ELATE (Extended Low-Intensity Anticoagulation for Thromboembolism) trial[26] has been criticised for using a non-standardised approach to INR evaluation and it had a lower rate of major bleeding than other trials using full intensity warfarin. In turn, the PREVENT trial[25] has been criticised because the actual numbers of bleeding events were so low and it is difficult to make sound statistical conclusions from them. Although ximelagatran is not yet approved for this indication, it offers a third option that will eventually need to be compared with extended warfarin therapy. One approach to clinical practice is to discuss the results of the recent studies with individual patients. In a patient with no risk of major bleeding, long-term anticoagulation with full intensity oral vitamin K antagonist may offer the best protection against a recurrent VTE, while low inten-

Table II. Comparative outcomes of venous thromboembolism (VTE) or major bleeding with extended anticoagulation therapy

Parameter	PREVENT[25]	ELATE[26]	THRIVE[29]
Number of patients	508	738	1223
Mean follow-up (y)	2.1	2.3	1.5
VTE recurrence (per 100 patient-years)			
Placebo	7.2		8.4
Low-dose warfarin	2.6	1.9	
Full-dose warfarin		0.7	
Ximelagatran			1.9
Major bleed (per 100 patient-years)			
Placebo	0.4		0.9
Low-dose warfarin	0.7	1.1	
Full-dose warfarin		0.9	
Ximelagatran			0.7

ELATE = Extended Low-Intensity Anticoagulation for Thromboembolism; **PREVENT** = Prevention of Recurrent Venous Thromboembolism; **THRIVE** = THRombin Inhibitor in Venous ThromboEmbolism.

sity therapy remains a reasonable choice, depending on the individual patient and their risk of bleeding.

4. D-Dimer and Residual Vein Thrombosis

The question about providing extended anticoagulation depends in part on identifying those patients who are at highest risk of recurrence, as they would benefit most from extended anticoagulation. D-Dimer has been shown to be helpful in this regard. In a prospective cohort study of 610 patients with a first episode of idiopathic DVT, patients treated for a minimum of 3 months with oral anticoagulants had a D-dimer measured 3 weeks following the discontinuation of anticoagulation.[33] There was a 60% lower relative risk of VTE recurrence in patients with a D-dimer level of less than 250 ng/mL compared with higher levels. In another series of 608 patients with first-time proximal DVT, D-dimer levels were measured at the time of oral anticoagulant discontinuation and 90 days afterwards in conjunction with residual vein thrombosis seen on ultrasonography.[34] In patients without residual vein thrombosis, a positive D-dimer (defined as greater than 500 ng/mL) was associated with an 8.3% rate of recurrent events compared with 3.4% in patients with a negative D-dimer. Residual vein thrombosis and a positive D-dimer were associated with a 16.5% risk of recurrence. One series using residual vein thrombosis alone as a predictor of recurrent clots found it to be a useful marker.[35] Patients with symptomatic proximal DVT were studied with serial ultrasonographic evaluation at 3 months after the acute event and then repeated at 6, 12, 24 and 36 months if the initial ultrasound showed residual thrombosis. Recurrent VTE was more common in patients who had persistent vein thrombosis with an HR for a recurrent event of 2.9 (95% CI 1.6, 5.2; $p = 0.001$). Making predictions as to which patients will have recurrent thrombosis and what markers or physical findings are predictive is still investigational and needs further study before entering the realm of routine clinical practice.

5. Conclusion

Many unanswered questions remain on the use of extended oral anticoagulation. Identifying patients at risk for recurrence can help target therapy to those who would benefit most from extended anticoagulation, and markers such as the D-dimer and residual vein thrombosis may be powerful tools for predicting recurrence. Future directions in the treatment of venous thromboembolic disease are likely to include use of newer anticoagulants and a better assessment of the probability of recurrent VTE using both risk factors and markers such as D-dimer. Until such time, current evidence indicates that full dose warfarin titrated to a goal INR of 2–3 offers the best protection against recurrent thromboembolism without an apparent increase in major bleeding compared with low intensity warfarin therapy in the context of a clinical trial. However, one must assess the risk of bleeding on an individual basis and the quality of long-term INR measurement before considering long-term extended full intensity or low intensity therapy. The latter may offer greater safety and ease of monitoring for selected patients.

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