Anticoagulation or Inferior Vena Cava Filter Placement for Patients With Primary Intracerebral Hemorrhage Developing Venous Thromboembolism?

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Background—Most patients with primary intracerebral hemorrhage developing clinically apparent proximal deep vein thrombosis (DVT) and/or pulmonary embolism (PE) require treatment with either anticoagulants or inferior vena cava filter insertion. Although the latter probably reduces the immediate risk of incident or recurrent PE and surmounts the undefined risk of recurrent intracranial bleeding with anticoagulation, the issue of preventing further thrombus propagation is not addressed, and there are associated short- and long-term risks, including a greater incidence of recurrent DVT.

Summary of Review—There are no data from randomized trials to clarify optimum treatment in these patients; indeed, the feasibility of such studies is questionable. Hence, treatment decisions continue to be made on an individualized basis and should include assimilation of information on key factors such as time elapsed post-stroke and lobar versus deep hemispheric location of the index event, natural history studies demonstrating a two-fold risk of recurrent intracerebral hemorrhage in the former subgroup.

Conclusions—In patients selected for anticoagulation, data from nonstroke patients suggest that a 5- to 10-day course of full-dose low-molecular-weight heparin followed by 3 months of lower-dose low-molecular-weight heparin is at least as effective as warfarin and may be associated with fewer hemorrhagic complications. (Stroke. 2003;34:2999-3005.)

Key Words: deep vein thrombosis | intracerebral hemorrhage | pulmonary embolism
given that aspirin, which reduces clinical PE by 29% after AIS,13 is not used after PICH, the incidence of recognized, clinical VTE in the first month after PICH is likely to be ≥2% to 3%.

Approximately 125,000 first or recurrent strokes occur annually in the United Kingdom.14 PICHs account for ≈10% of these15 and are associated with a 30-day mortality of 35% to 50%.9,16 Hence, clinical VTE occurs in several hundred persons with PICH annually in the United Kingdom, and perhaps 100 to 200 people with PICH succumb to PE.

Treatment Decisions in Patients With VTE After PICH: Playing the Odds

Treatment decisions in patients with PICH developing clinical VTE are currently made on an empirical individual basis and entail evaluating the following factors: the expected morbidity and mortality in patients with PICH and VTE that is left untreated, the expected effectiveness of treatment with anticoagulation or IVC filter insertion on these end points, and the expected morbidity and mortality associated with either treatment option. The magnitude of each of these specific factors is uncertain. In some cases, an approximation may be arrived at by extrapolation of data from unselected patients, eg, the likely mortality from incident or recurrent PE associated with untreated DVT or PE; in others, there are few meaningful data to guide decision making, as when attempting to estimate the risk of recurrent intracerebral bleeding when anticoagulants are given after PICH. What is known about each of these factors is discussed next.

Morbidity and Mortality Associated With Untreated Clinical VTE After PICH

An estimate of the morbidity and mortality that might be associated with untreated clinical VTE after PICH is central to the formulation of appropriate treatment decisions. Although no such data are available specifically for patients with PICH, data on the natural history of untreated clinical VTE are available from historical series of unselected general medical and surgical patients reported before 1960, before which anticoagulants were not considered mandatory after VTE. Pooled data from a number of such studies containing several thousand patients with clinical PEs and DVTs (which are proximal in most cases17,18) show that the overall risks of fatal PE in untreated PE (recognized and in whom survival to the point of diagnosis occurred) and treated PE were 26.6% and 2.6%, respectively, with corresponding figures for proximal DVT (PDVT) of 16.2% and 0.7%. Recurrent nonfatal PE occurred in 12.8% and 15.1% of untreated patients presenting with PE and DVT, respectively19 (see the Figure).

Two caveats should be kept in mind when these data from the preimaging era are interpreted. First, all cases of VTE were diagnosed clinically. Subsequent studies using objective diagnostic methods found that VTE was confirmed in fewer than half of the patients in whom it was suspected,20–22 so early series contain a proportion of patients with diagnoses other than VTE. It should be noted, however, that alternative diagnoses in patients presenting with symptoms suggestive of DVT are rarely life threatening, whereas those in patients presenting with symptoms suggesting PE, such as pneumonia and myocardial infarction, may well be. Therefore, early data probably do not overestimate the mortality associated with untreated DVT, but the situation regarding PE is less certain. Second, all of these series were retrospective; no information was given on how patients were selected for anticoagulation or conservative measures; and treatment regimes varied widely, in some cases consisting of only a few days’ therapy with heparin. Moreover, nonanticoagulated patients were kept on bedrest for periods of up to 40 days,23 which may have worsened outcomes.

Notably, several studies indicate that the case fatality rate of clinical PE in unselected (ischemic and hemorrhagic) stroke patients may be higher than in other clinical settings.24–26 Hence, on the basis of these data, it seems reasonable to conclude that untreated clinical PDVT after PICH would be associated with ≥10% to 20% risk of fatal PE and 10% to 20% risk of nonfatal clinical PE; corresponding figures for untreated recognized clinical PE would be ≥20% to 30% and 10% to 20%. A further concern in survivors of untreated VTE is the association with the postthrombotic syndrome, which was almost universal in patients surviving untreated clinical PDVT in historical series,27 the incidence of which has dropped to ≈30% in the anticoagulant era.28

From these data, a policy of leaving unselected patients with PICH thought to have an otherwise reasonable prognosis who develop clinical VTE untreated is unacceptable. However, given the likely risks associated with both anticoagulation and IVC filters in these patients, might it be possible to identify selected subgroups with VTE in whom an observational brief might be justified?

Withholding Treatment in Selected Patients With PICH and Clinical VTE

Observation only is probably justified in 1 subgroup of patients with clinical DVT and might be justified in another with PE. Ten percent to 20% of clinical DVTs are below the knee as opposed to proximal.17,18 Although PEs can arise from nonextending below-knee DVTs,29 they are very unlikely to be life threatening in the presence of adequate
cardiorespiratory reserve (Table), with an incidence of clinically important PE of probably ≈1% in untreated cases. Hence, PDVT and below-knee DVT are subgroups with distinct prognoses, and the main concern in patients with isolated below-knee DVT is the 20% risk of proximal propagation in untreated cases. Although it would be usual to treat selected patients with symptomatic below-knee DVT, withholding treatment is considered safe if cardiopulmonary reserve is adequate (enabling them to survive a potential small PE from a below-knee source) as long as serial noninvasive imaging over the next fortnight excludes proximal propagation. Hence, given the potential risks associated with treatment, observation only would be reasonable in patients with PICH and clinical DVT confined to below the popliteal vein as long as cardiorespiratory reserve was adequate and ultrasound at 1 and 2 weeks did not show propagation to the proximal segment.

Two recent major studies have suggested that it may be possible to identify a subgroup of good-prognosis patients with PE who may have a relatively benign outlook in the absence of treatment and highlight the prognostic importance of residual PDVT and cardiopulmonary reserve. Hull et al withheld treatment in 627 patients from a larger cohort of untreated patients presenting with clinically suspected PE who had indeterminate ventilation-perfusion (VQ) scans, adequate cardiopulmonary reserve (Table), and serially negative impedance plethysmography for residual PDVT over a 2-week period. Recurrent VTE occurred in only 1.9% at 3 months, including 1 fatal PE. Subsequently, Wells et al investigated a cohort of 665 patients with nonhigh clinical suspicion for PE, indeterminate VQ scans, and negative serial ultrasound examinations for PDVT over 2 weeks (performed on days 1, 3, 7, and 14) and showed that the 3-month incidence of clinical nonfatal VTE was only 0.5%. Both of these studies contained inpatients and outpatients, including a proportion with immobility, and clearly a significant minority of patients in whom treatment was withheld had sustained a PE. Stein et al retrospectively combined data from these reports to show that patients with nonmassive PE, adequate cardiopulmonary reserve, and negative serial ultrasounds over 2 weeks who were left untreated could be expected to have 3-month incidences of fatal and nonfatal recurrent PE of 0% and 3% and concluded that good-risk patients with PE who are at high risk of bleeding might safely be left untreated, an approach requiring prospective validation. Hence, withholding treatment in patients with clinical PE after PICH who fulfill these criteria might be an acceptable option, although it remains untested.

How Effectively Do IVC Filters Prevent Morbidity and Mortality in Clinical VTE?

The effectiveness of anticoagulants in the treatment of VTE was first demonstrated in 1960 by Barratt and Jordan, who randomized 35 patients with PE to anticoagulation plus bedrest or bedrest only. Five of 19 untreated patients (26.5%) died of recurrent PE, and another 5 (26.5%) developed nonfatal recurrence, where 0 of the 16 treated patients developed PE (for recurrent fatal and nonfatal PE, \( P = 0.0005 \)). However, although widely cited as supporting the effectiveness of anticoagulation in patients with VTE, the methodology of the trial has been criticized on a number of counts, so the main evidence for the effectiveness of anticoagulants is derived from a comparison of the outcomes of untreated VTE in historical series to treated VTE in historical and modern series (data summarized in Reference 19).

The historical data have been discussed. The best data on the outcome associated with treated VTE in untreated patients in the modern era come from an overview of 25 prospective studies published between 1966 and 1997 reporting on outcomes in patients with objectively diagnosed clinical VTE treated with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by oral anticoagulants for 3 months. Data were available on 4221 patients presenting with DVT and 1302 with PE. During 3 months of treatment, 0.4% and 1.5%, respectively, suffered fatal PEs. In addition, 3.8% of patients presenting with DVT developed nonfatal recurrent VTE over this period, although comparable data were not available for those presenting with PE. In a more recent study of 1021 patients with VTE treated with either UFH or LMWH followed by oral anticoagulants for 3 months, recurrent fatal PE occurred in 2.2% of patients presenting with PE versus 0% of those presenting with DVT, whereas recurrent nonfatal events occurred in 4% and 5%, respectively. Pooled data from these studies show that treated patients presenting with DVT have a 3-month risk of fatal and nonfatal PE of 0.3% and 3.9%, respectively; corresponding figures in patients presenting with PE are 1.7% and 4.1%. Hence, fatal PE is an uncommon event in patients with VTE once anticoagulants are begun (outcomes of untreated/treated VTE are illustrated in the Figure).

How Effectively Do IVC Filters Prevent Morbidity and Mortality in Clinical VTE?

IVC filters have been available for >3 decades and have been inserted percutaneously since 1984. The principal indication for placement is a strict contraindication to or failure of anticoagulant therapy. The only randomized trial of filters was performed by Decousus et al, who randomized 400 patients with symptomatic PDVT with or without concomitant symptomatic PE considered to be at high risk of incident or recurrent PE to treatment with anticoagulants alone or in combination with IVC filter placement; 4 different kinds of filters were used, and anticoagulants were given for ≥3 months. VQ scanning with or without pulmonary angiography was performed at baseline and 8 to 12 days later.
Although PE (symptomatic plus asymptomatic) between days 8 and 12 was significantly more common in the anticoagulant only group (4.8 versus 1.1% p: 0.03), the difference in symptomatic events was not significant; cumulative symptomatic PE at 24 months did not differ significantly between the groups (3.4% versus 6.3% favoring the IVC filter group); and overall 2-year mortality was similar. Furthermore, the cumulative incidence of recurrent DVT at 2 years was significantly higher in the filter group at 20.8% versus 11.6% (P=0.02). Hence, although IVC filters may reduce the short-term risk of PE in patients receiving concomitant anticoagulation, this reduction comes at the cost of increasing the long-term risk of recurrent DVT if long-term anticoagulation is not used.

Most of the data on the risks and benefits of IVC filters come from predominantly retrospective reviews of case series containing variable proportions of patients not given anticoagulants. Streiff et al recently reviewed the literature on the 5 types of filters available in the United States with mean follow-ups of 6 to 18 months and found that symptomatic PE occurred in 2.6% to 3.8%, but no type of filter could be identified as superior because of the absence of randomized comparisons. Although these data support the concept that IVC filters reduce (but do not eliminate) the risk of PE, there have been no studies comparing the effectiveness of IVC filters (without anticoagulation) in the main patient group of interest—those in whom filters are used as an alternative to anticoagulation.

### Risks Associated With Anticoagulation in Patients With VTE After PICH

In unsolicited patients with VTE, the excess risk of intracranial bleeding associated with a 3-month course of treatment with anticoagulants is $\approx0.1\%$, although the equivalent risk in patients with PICH is unknown. However, the annual baseline risk or recurrent ICH in patients presenting with an index PICH is known.

In a systematic review$^{53}$ of 10 prospective studies published between 1982 and 2000 investigating the natural history of recurrence in 1880 patients with PICH who survived for $\approx30$ days and were followed for a mean of 3.4 years, the annual rate of recurrent ICH was 2.3%. The only factor that consistently predicted a higher recurrence rate was lobar location of the incident event. On the basis of data from 1015 patients in 4 studies, patients with lobar hemorrhage had higher annual recurrence rates of 4.4% (95% confidence interval [CI], 3.1 to 6.3) versus 2.1% (95% CI, 1.6 to 2.7) in patients with deep hemispheric hemorrhages ($P=0.002$), presumably reflecting a higher incidence of underlying cerebral amyloid angiopathy in the former group.$^{54,55}$ Recurrent intracranial hemorrhage had a higher mortality than the index event at $\approx70\%$. Only 3 of the studies provided data on recurrence rates over time$^{54,56}$ which were generally higher in the first year or 2 after the index bleed than in subsequent years. Two of these studies provided data on recurrence rates in the first 3 or so months from stroke onset. In the Oxford Community Stroke Project, 1 of 66 patients (1.5%) with PICH rebled in the first 3 months$^{5}$; in the other study, 4 of 989 patients (0.4%) rebled within 4 months of onset.$^{56}$ Pooling these data gives a 0.5% recurrence rate in the first 3 to 4 months after PICH. Approximately 25% of the patients in these studies had lobar PICH compared with 75% with deep hemispheric PICH. The relationship between location of the index bleed in the brain stem or cerebellum, which accounts for $\approx10\%$ to 15% of PICHs,$^{54,57-62}$ and risk of rebleeding was not examined, although in 1 study published subsequent to this systematic review, it was associated with a similar risk of rebleeding to the group as a whole.$^{61}$

The only prospective study of anticoagulants after PICH included 46 patients randomized to UFH 5000 U tid started on either day 4 or 10 after onset and given for an unspecified period of time.$^{63}$ The latter subgroup were considered controls because this strategy was standard practice on the unit before the trial. Three of 23 controls rebled compared with 1 of 23 patients given UFH on day 4; all cases of rebleeding were associated with a fatal outcome. The authors concluded that low-dose UFH started on day 4 “did not increase the risk of re-bleeding” compared with standard practice. However, this study provides no information about the safety of low-dose UFH after PICH because there was no placebo group, so results could be interpreted as showing that both regimes were equally safe or equally unsafe. Subsequently, another 22 patients were added to this series who were treated from day 2 after onset$^{64}$ with no additional cases of rebleeding. Given the absence of a placebo group, very small sample size, and different dosing regimen used, these data provide little useful information on the issue of the safety of using full-dose anticoagulants after PICH.

A single retrospective study provides limited information about outcomes in patients with intracranial bleeding given full-dose anticoagulants. In a study of patients with first PICH admitted to 3 hospitals between 1986 to 1995 who returned to their own homes,$^{61}$ a subgroup of 22 patients started on anticoagulants after the index admission (5 for prosthetic heart valves, 4 for atrial fibrillation, 10 for arterial occlusive disease, and 3 for PE) was identified. More than half of the patients who survived were discharged to nursing homes, and these patients were excluded from the study. The odds ratio for recurrent intracerebral hemorrhage was 2.7 (95% CI, 0.9 to 7.8) in this subgroup. However, these data are of very limited value in predicting anticoagulant risk in patients with PICH because the patients studied were a selected group with good outcome and may have been at lower risk of anticoagulant-associated intracranial bleeding because incident hematoma size strongly correlates with outcome.$^{57,59,62}$ Furthermore, no information was given as to how patients were selected for anticoagulation, and the subgroup receiving anticoagulants was very small.

Finally, prospective and retrospective studies have shown that low-dose heparin is safe in neurosurgical patients$^{65}$; small retrospective series have shown that low-dose heparin appears safe in patients with traumatic brain injury$^{66}$ and that full anticoagulation appears to be acceptably safe in patients with intracranial malignancy$^{67-71}$ who develop VTE and when given to patients with cerebral venous sinus thrombosis associated with ICH.$^{72}$ Furthermore, experiments with rats have shown that the risk of intracranial bleeding after craniotomy with full anticoagulation falls progressively as the
number of days after surgery increases and that anticoagulation can safely be started 10 to 14 days postoperatively.7,31

The risks of extracranial bleeding when anticoagulants are given to patients who develop VTE after PICH are unknown. However, the risk of major bleeding in an overview of 11 studies of unselected patients with VTE anticoagulated for 3 months was ≈3%, the great majority of which were extracranial.74 The risk of bleeding is greatest during the first month of treatment.52 Furthermore, not all bleeds may be attributable to anticoagulation itself.32

In summary, the only conclusion that can be drawn from these data is that the risk of intracranial bleeding associated with a 3-month course of anticoagulants after PICH is an unknown multiple of the baseline risk of rebleeding. In patients presenting with nonlobar PICH, this baseline risk may be ≈0.5%.56 In those with a lobar index PICH, this risk may be approximately twice as high53 at ≈1%. Hence, treatment of clinical VTE after PICH with anticoagulants could result in a spectrum of risk-to-benefit ratios ranging from substantial benefit to possible harm.

Is Treatment of VTE With Therapeutic-Dose LMWH Safer Than Treatment With Oral Anticoagulants?

Data from 6 studies75–80 containing 1184 patients with DVT (20% of whom also had signs or symptoms of PE) comparing treatment of VTE with 5 to 10 days of full-dose LMWH or UFH followed by oral anticoagulation with warfarin or acenocoumarol or with lower-dose LMWH maintenance therapy (eg, enoxaparin 40 mg once daily76,78,79) for ≥3 months were pooled in a meta-analysis in 2001.81 In patients receiving maintenance LMWH, odds ratios for recurrent DVT and PE were 0.77 (95% CI, 0.43 to 1.35) and 0.6 (95% CI, 0.24 to 1.49); those for major and minor bleeding were 0.73 (95% CI, 0.28 to 1.91) and 0.28 (95% CI, 0.16 to 0.48). Recurrent VTE between 4 and 12 months occurred in 7.7% of the LMWH group compared with 5.2% of the oral anticoagulants group (odds ratio, 1.6; 95% CI, 0.8 to 3.0). In a subsequent study,82 146 patients with DVT and/or PE and cancer—a subgroup at particularly high risk of both recurrent VTE and bleeding—were randomized to 3 months of treatment with enoxaparin (1.5 mg/kg once daily) or initial treatment with enoxaparin followed by 3 months of warfarin. Major hemorrhage or recurrent VTE occurred in 15 of the warfarin-treated patients (21.1%) versus 7 (10.5%, P=0.09) of the enoxaparin group, including fatal bleeding in 6 (8.0%) versus 0 (P=0.03). Two other studies published subsequent to the meta-analysis show concordant results.83,84 These data raise the possibility that the predictable anticoagulant response with LMWHs might make them a theoretically attractive alternative to warfarin in the ongoing treatment of VTE in patients at high risk of bleeding and/or recurrence.80,81,85 Hence, although definitive data are lacking, LMWH might be considered an alternative to warfarin when VTE occurs after PICH.

Risks Associated With IVC Filter Placement in Patients With VTE After PICH

The increased long-term risk of DVT in the trial of Decousus et al15 has been discussed. Examination for filter patency was performed in the 37 patients with filters who developed symptomatic recurrent VTE during the 2-year period of this study, and filter thrombosis was found in 16. In the overview by Streiff,1 DVT (clinical and subclinical) occurred in 6% to 32% of patients with filters, IVC filter thrombosis in 3.6% to 11.2% (clinical and subclinical), and symptomatic insertion site thrombosis in 7% to 17%. Filter migration, IVC penetration, or filter fracture occurred in a minority of patients who underwent radiological surveillance, although events were rarely symptomatic. Postthrombotic syndrome, which can have a significant negative impact on quality of life,86,87 is a further potential complication, although follow-up has generally been too short to ascertain its incidence accurately. In another review, it was found that filter-related complications were rarely life threatening, with deaths caused by filter complications occurring in 0.16% of patients in the reviewed studies.50

Is a Trial of Anticoagulation Versus Filter Placement in VTE After PICH Feasible?

Resolution of uncertainty about optimum treatment of patients with PICH and clinical VTE would require a multicenter trial in which patients were randomized to either treatment with anticoagulation or IVC filter placement with follow-up to ascertain recurrent VTE, intracranial and extracranial bleeding, overall mortality, and the proportion of patients treated with filters who subsequently require anticoagulation because of recurrent thrombosis. Longer-term follow-up is required to monitor rates of recurrent DVT and postthrombotic syndrome. However, there are 2 major difficulties in performing such a trial.

First, patients with PICH who develop clinical VTE are relatively rare. The average district general hospital would be expected to admit 30 to 40 patients with PICH annually,16 up to half of whom die within the first month.9 Hence, 1 case of PICH complicated by clinical VTE might be encountered every 1 to 2 years in such a hospital. Therefore, cooperation from a large number of centers would be required, and maintaining enthusiasm for such a study over a prolonged period of time would be highly problematic.

Second, a simple strategy of randomization to anticoagulation or filter placement that did not take into account factors likely to influence the risk of recurrent intracranial bleeding such as lobar or nonlobar location of PICH and time elapsed since the index event would arguably belie the complexity and individualization of the decision-making process in these patients. Furthermore, an attempt to address this by applying a trial to a more targeted subgroup would further compound the problem of recruitment. Considering all of these factors, the feasibility of such a trial seems doubtful.

Conclusions

There is no immediate prospect of resolving uncertainty about the optimum treatment of clinical VTE on a background of PICH in a randomized trial. However, prospective data derived in unselected patients on such issues as identification of good-prognosis patients with PE in whom treatment could safely be withheld, the short- and long-term safety and effectiveness of IVC filters as an alternative to antico-
agulants, and alternatives to warfarin for the secondary prevention of VTE are likely to be forthcoming and may help inform treatment decisions. In the interim, clinical management decisions will continue to be individualized and frequently difficult.

References

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