

Safety and Cost of Low-Molecular-Weight Heparin as Bridging Anticoagulant Therapy in Subacute Cerebral Ischemia

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Background and Purpose—Anticoagulation with intravenous unfractionated heparin (IVUH) while awaiting therapeutic oral anticoagulant levels is a common practice in patients with acute and subacute cerebral ischemia. A promising alternative strategy is to use bridging subcutaneous low-molecular-weight heparin (LMWH), which may have a favorable risk-benefit profile compared with IVUH and may permit earlier discharge with completion of transition to warfarin therapy as an outpatient.

Methods—A LMWH, enoxaparin 1 mg/kg BID, was used as bridging anticoagulation therapy in 24 consecutive patients admitted to a university stroke center in whom the treatment plan included transition from acute to chronic anticoagulation. The LMWH group was contrasted with the preceding 24 patients transitioned to warfarin with IVUH at the same center.

Results—Fewer patients in the LMWH bridging therapy group experienced neurological worsening than in the IVUH bridging therapy group (2/24 versus 8/24; $P=0.033$). Fewer total adverse events were noted in the LMWH group than in the IVUH cohort (3 versus 20; $P=0.002$). Fifteen of the 24 LMWH patients (62.5%) were discharged while still receiving LMWH and completed transition to warfarin as outpatients, receiving an average of 3.6 days of outpatient transitional therapy. In these 15 patients, use of LMWH was associated with a net savings of \$2197 per patient.

Conclusions—In this pilot cohort with subacute cerebral ischemia, bridging LMWH appeared to be safer than bridging IVUH and was associated with reduced hospital stay and reduced total cost of care. (*Stroke*. 2000;31:2563-2568.)

Key Words: anticoagulants ■ atrial fibrillation ■ costs and cost analysis ■ heparin

Long-term anticoagulation is effective in the prevention of recurrent stroke in atrial fibrillation¹⁻⁴ and also commonly pursued for secondary stroke prevention in other cerebral ischemia patients, including those with other cardiac sources of embolism, intracranial stenosis, cervicocerebral dissection, hypercoagulable states, and recurrent ischemia on antiplatelet agents.⁵⁻⁸ Whether acute anticoagulation confers net benefit or harm in individuals with new-onset cerebral ischemia has not yet been adequately defined by randomized clinical trials. Recent large-scale trials, like smaller older studies, have yielded conflicting results, likely in part because of use of different agents, doses, and routes of administration.⁹⁻¹⁵ One current US national guideline states that no recommendation on the optimal use of anticoagulation in acute ischemic stroke can presently be formulated.¹⁶ Another recognizes acute anticoagulation as a treatment option, especially for those patients with large-artery atherosclerotic disease, cardioembolic source, and stroke in progression.¹⁷

A common practice is to initiate anticoagulation with a continuous intravenous infusion of unfractionated heparin

(IVUH) within the first 72 hours of stroke or transient ischemic attack onset in patients with small to moderate cerebral infarcts and to initiate anticoagulation 5 to 9 days after stroke onset in patients with large cerebral infarcts.¹⁸⁻²⁰ Consequently, many patients with stroke or crescendo transient ischemic attacks are anticoagulated with IVUH early during their acute hospitalization and then receive overlapping IVUH and warfarin to transition to long-term oral warfarin therapy before discharge.

Hospital stays may be prolonged by the practice of using IVUH during bridging therapy from acute to long-term anticoagulation. Patients sometimes remain in the hospital well after neurological stabilization has been achieved and a diagnostic work-up completed, solely for the purpose of receiving intravenous heparin until a therapeutic international normalized ratio (INR) has been achieved. Despite its common use, the financial costs of bridging IVUH, including the frequency and duration of extensions of hospital stay, have not previously been characterized. The use of IVUH for ischemic stroke in general has been shown to be associated with increased costs of care.²¹

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An alternative to IVUH as a bridge to long-term anticoagulation is subcutaneous injection of low-molecular-weight heparin (LMWH) at doses effective for arterial disease. These compounds have several theoretical advantages over IVUH, including a long half-life resulting in once or twice daily dosing, predictable anticoagulation effect so that anticoagulation intensity monitoring is not required, reduced incidence of heparin-induced thrombocytopenia, and reduced incidence of adverse bleeding events.^{22–25}

Clinical trials have demonstrated that high-dose subcutaneous LMWHs are more efficacious and are associated with fewer side effects than IVUH as bridging therapy to warfarin in patients with established deep venous thrombosis.^{24,26,27} In addition, in established deep venous thrombosis patients, LMWHs permit earlier hospital discharge and reduce overall costs of care.^{28,29} High-dose subcutaneous LMWHs have recently also been found to be more efficacious and safer than IVUH in treating arterial thromboses in the coronary bed,^{30–33} leading to Food and Drug Administration approval of the use of high-dose LMWH for patients with unstable angina and non-Q wave myocardial infarction. These studies in noncerebral circulations suggest that high-dose subcutaneous LMWH may be superior to IVUH as a bridge to long-term anticoagulation in ischemic stroke patients. Three clinical trials have tested LMWHs versus placebo as an immediate treatment strategy for acute ischemic stroke, one showing a significant benefit, the others no net benefit or harm.^{10,13,14} However, the patients in these studies are not fully comparable to the subacute ischemic stroke patients in whom bridging therapy to warfarin is used, a select subset of patients who generally are further out from stroke onset and who are considered by their treating physicians to be stable enough for initiation of long-term anticoagulation. A recent meta-analysis of randomized, controlled trials of LMWHs and heparinoids in stroke patients found a statistically significant benefit of therapy when treatment was started >24 hours after stroke onset.³⁴

The purpose of our study is to explore the safety and cost of using LMWH rather than IVUH as bridging anticoagulant therapy to long-term anticoagulation in cerebral ischemia patients.

Subjects and Methods

Subjects

Patients Treated With LMWH

Data on patients treated with LMWH was collected from 1997 to 1999, when the treatment policy on the University of California at Los Angeles Stroke Unit was to use LMWH for bridging anticoagulation in all patients meeting the following criteria. Inclusion criteria were as follows: clinical diagnosis of transient ischemic attack or cerebral infarction and wish of the attending neurologist to pursue a treatment plan of acute followed by chronic anticoagulation. Exclusion criteria were as follows: medical condition requiring treatment with IVUH; active bleeding; anemia; major operative procedure in last 24 hours; uncontrolled hypertension with systolic blood pressure >220 mm/Hg or diastolic blood pressure >120 mm/Hg; renal, hepatic, respiratory, or cardiac failure; hypersensitivity to heparin compounds; known or suspected infectious endocarditis; pregnancy; or coma.

Patients Treated With IVUH

For comparison, data were collected on consecutive patients treated from 1996 to 1997, when the treatment policy on the University of California at Los Angeles Stroke Unit was to use IVUH for patients with transient ischemic attack or ischemic stroke who were receiving bridging anticoagulation.

Treatment Regimen

LMWH patients received enoxaparin 1 mg/kg SC BID. Warfarin was initiated on the same day as start of LMWH therapy. If the workup was complete and the patient could be discharged, LMWH therapy was continued at home or in a rehabilitation center. Enoxaparin was administered by nurses if the patient was hospitalized and by the patient, family members, friends, or home health nurses if the patient was discharged. IVUH patients received continuous intravenous heparin administered at doses chosen by the attending and the resident team. Partial thromboplastin times (PTTs) were generally obtained every 6 hours, and infusion rate was adjusted for a target PTT of 1.5 to 2.0 times control. Warfarin dosing was at the discretion of the attending and the resident team taking care of the patient and not based on prespecified algorithms. Long-term target INRs used for adjusting warfarin dosages were generally 2.0 to 3.0 (3.0 to 3.5 for patients with antiphospholipid antibody syndrome, 3.0 to 4.0 for patients with mechanical prosthetic cardiac valves). However, treating teams typically accepted an INR ≥ 1.8 as adequate for the discontinuation of LMWH or IVUH and continuation on warfarin alone.

Outcome Measures

Demographic information, stroke risk factors, anticoagulation parameters (anticoagulation indications, PTT, INR values, and number of days on anticoagulation), and therapy parameters (days to initiation of therapy and disposition) were collected on all patients. Demographic information, stroke risk factors, and anticoagulation indications were compared between the 2 groups by nonparametric tests for significant differences with the χ^2 test. In patients with infarcts, lesion size based on largest lesion diameter was categorized according to a modification of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) method: small (<0.5 cm), intermediate (0.5 to <1.5 cm), moderate (1.5 to <3.0 cm), large (>3 cm, unilobar), and massive (multilobar).¹²

Adverse events related to anticoagulation were noted and classified into the following categories: hemorrhagic transformation of infarct, neurological worsening, epistaxis, hematuria, guaiac-positive stool, subcutaneous hematoma, thrombocytopenia, phlebitis, and other. If LMWH therapy was completed after discharge, a telephone interview was conducted at end of therapy to assess for adverse events. Adverse events were compared between the 2 groups by nonparametric tests for significant differences by the χ^2 test. For LMWH patients, the National Institutes of Health Stroke Scale was performed daily during hospitalization, and the modified Rankin Scale and Barthel Index were performed at admission (premorbid) and at hospital discharge.

All financial analyses were performed with true cost data rather than charge data. Cost information was obtained from the hospital administration's Product Line Management System. Drug supply costs included \$3.11 per heparin bag and \$12.78 per 30-mg syringe of enoxaparin. Costs for laboratory monitoring of heparin were calculated by multiplying the number of PTTs ordered while the patient was on heparin by the cost of 1 PTT (\$19.63). Costs for hospital bed were estimated by using a mean acuity level bed cost for a nonmonitored, semiprivate bed (\$655). Cost for a home nursing visit for enoxaparin administration was \$100. In addition to performing cost calculations for the bridging dosing strategies actually used in these patients, we also performed an analysis of costs that would have been incurred had a conservative strategy of a minimum of 5 days of IVUH or LMWH warfarin overlap been followed in all patients.³⁵

TABLE 1. Cohort Characteristics

	LMWH	IVUH
n	24	24
Age (range), y	66 (40–92)	69 (29–90)
Female	50%	54%
Stroke	79%	75%
Transient ischemic attack	21%	25%
NIHSS score (range)	4.3 (0–17)	N/A
Antiplatelet agent on admission	46%	67%
Warfarin on admission	12%	4%
Treatment with tPA	21%	0%*
Past medical history		
Hypertension	58%	58%
Coronary artery disease	21%	25%
Previous stroke	17%	21%
Diabetes	17%	8%
Atrial fibrillation	12%	29%
Anticoagulation indications		
Intracranial atherosclerosis	38%	29%
Cardioembolism	33%	58%
Dissection	17%	4%
Cryptogenic stroke	4%	4%
Hypercoagulable state	4%	0%
Aortic arch atherosclerosis	4%	0%
Extracranial carotid artery stenosis	0%	4%

NIHSS indicates National Institutes of Health Stroke Scale; tPA, tissue plasminogen activator.

* $P=0.018$ (for all other variables, group differences did not reach statistical significance).

Results

Cohort characteristics, anticoagulation indications, and stroke risk factors are listed in Table 1 for the historical control group of patients treated with IVUH and the cohort treated with LMWH. The 2 groups were comparable in all respects, except for more frequent use of thrombolytic treatment in the LMWH cohort. Infarct size did not differ significantly between the cohorts. Among the 20 cerebral infarct patients in the IVUH cohort, lesion size was intermediate in 6, moderate in 7, and large in 7. Among the 19 cerebral infarct patients in the LMWH group, lesion size was small in 1, intermediate in 5, moderate in 6, and large in 7.

In the IVUH group, heparin was started on average on hospital day 1.3 (range, 0 to 9), and warfarin was begun on hospital day 2.1 (range, 0 to 10). Two patients received a heparin bolus (5000 U for one, 2500 U for the other). The remainder were started without a bolus at rates between 500 and 1000 U/h. Twenty-five percent of patients had their heparin drips discontinued temporarily for reasons other than high PTT levels (two thirds for an MRI, one sixth for another test, and one sixth for pulling out a central line). In the LMWH group, enoxaparin was started on average on hospital day 2.2 (range, 0 to 9) and postsymptom onset day 4.9 (range, 0 to 30), and warfarin was begun on hospital day 2 (range, 0 to 9).

TABLE 2. Adverse Events

	LMWH	IVUH
Neurological worsening	2 (8%)	8 (33%)*
Guaiac-positive stool	0	5 (20%)*
Gross hematuria	0	3 (13%)
Phlebitis	0	2 (8%)
Thrombocytopenia	0	2 (8%)
Arterial catheter site bleed	1 (4%)	0
Total events	3	20†
Total patients	3 (12.5%)	9 (37.5%)*

* $P<0.05$.

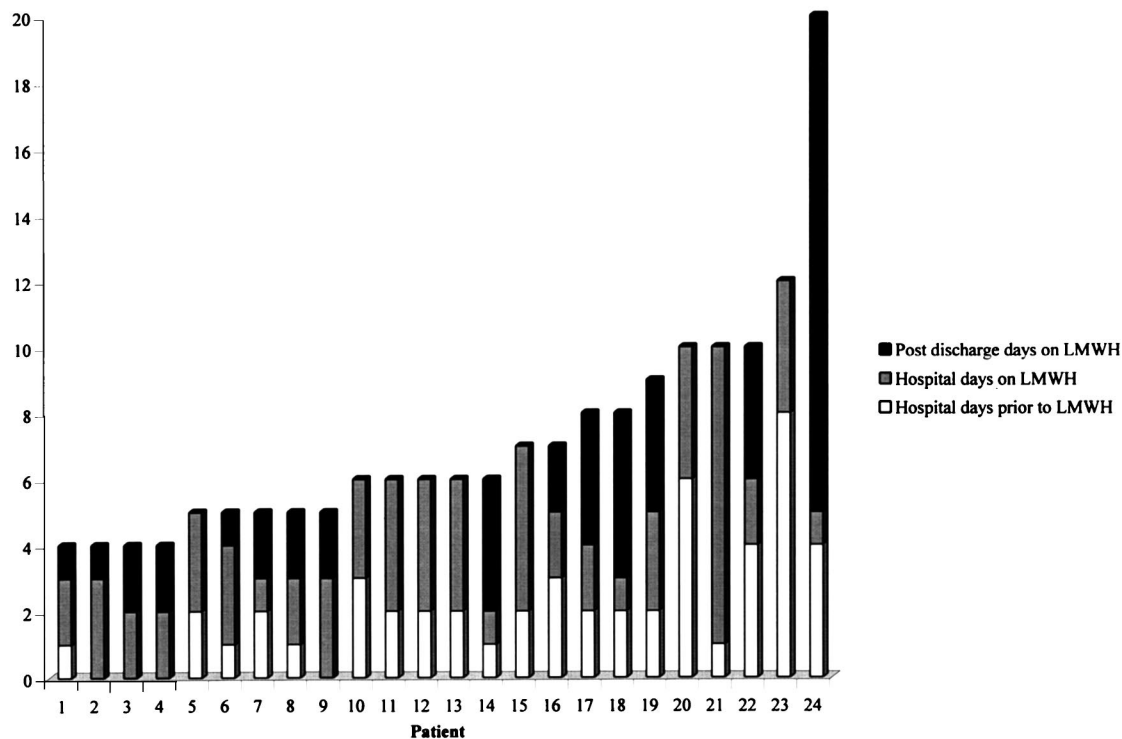
† $P<0.01$.

Warfarin was initiated with a 10-mg loading dose in 88% of the IVUH group and 67% of the LMWH group. Sixty-seven percent of patients in the IVUH group and 46% in the LMWH group received 10-mg loading doses of warfarin on both their first and second days.

Ninety-six percent of IVUH patients completed transition to warfarin while on the acute hospital service, with 1 patient discharged to a rehabilitation service while on heparin. The mean interval in the IVUH group from start of warfarin to achievement of a therapeutic INR was 3.3 days (range, 2 to 9, with 1 patient never achieving a therapeutic INR before discharge). Ten patients had INRs of <2.0 on the day of heparin discontinuation. In 63% of patients, hospital stay was extended solely because of need to complete IVUH transitioning to oral warfarin. Among these patients, the mean extended stay was 2.4 days (range, 1 to 4). Across the IVUH cohort, of 169 total days of hospitalization, 21% were solely for transitional IVUH.

In the IVUH group, the narrow target therapeutic range of PTT ratio 1.5 to 2.0 was achieved 36.8% of the time, and a broad therapeutic target range of 1.5 to 2.5 was achieved 53.6% of the time. When we considered the narrow therapeutic range, patients were underanticoagulated 33% of the time and overanticoagulated 30.4% of the time. Only 1 patient was maintained in the narrow therapeutic target range at every time point throughout hospitalization, and only 12.5% were maintained in the broad therapeutic target range at every time point.

Among the LMWH patients, 15 received only LMWH as an injectable anticoagulant, and 9 patients received IVUH acutely before the treatment plan of bridging to long-term anticoagulation was formulated and LMWH and warfarin begun. Fifty-four percent were discharged home while still receiving LMWH, 8% were discharged to rehabilitation on LMWH, and 38% completed transition to warfarin on the acute hospital service (Figure). The mean interval from start of warfarin to achievement of a therapeutic INR was 4.4 days (range, 1 to 20). Twenty-nine percent of patients had INRs of <2.0 on the day of enoxaparin discontinuation. Among the 15 patients who received LMWH as outpatients, the mean duration of LMWH therapy was 3.6 days (range, 1 to 15). Ninety-six percent of patients initiated on LMWH bridging therapy completed transition to warfarin while still on LMWH; in 1 patient who experienced worsening of neurological deficit while on LMWH,



Time course of LMWH treatment in individual patients.

enoxaparin was discontinued and IVUH substituted for the remainder of the transition.

Adverse events in the cohorts are shown in Table 2. No patients in either treatment group had hemorrhagic transformation of infarction, other central nervous system bleeding, major systemic bleeding, or death. Fewer patients had worsening of their neurological deficit, transiently or permanently, on LMWH than on IVUH (2 versus 8; $P=0.033$). Adverse events encountered only in the IVUH group included guaiac-positive stool, gross hematuria, phlebitis, and thrombocytopenia. An episode of bleeding from an angiogram catheter site was seen only in the LMWH group. Adverse events of any kind occurred less frequently in the LMWH group than the IVUH group (3 versus 20; $P=0.002$).

In the IVUH group, 88% of patients had physical and occupational therapy initiated during their acute hospitalization, on average on hospital day 4.3 (range, 2 to 11). Among these 21 patients, the presence of an intravenous line for administration of heparin constrained physical and occupational therapy interactions a mean of 2.9 days (range, 1 to 10). In the LMWH group, 58% of patients had physical and occupational therapy initiated during transition to warfarin, on average on hospital day 4.2 (range, 1 to 6). Among these 14 patients, the mean duration of physical and occupational therapy unconstrained by an intravenous line as a result of LMWH treatment was 1.8 days (range, 1 to 6).

Across the IVUH cohort, total cost of bridging anticoagulation was \$53 541, with a mean of \$2231 per patient. Hospital expenses accounted for 96.9% of these costs, PTT laboratory expenses for 2.9%, and heparin drug expenses for 0.5%. Across the entire LMWH cohort, total cost of bridging anticoagulation was \$51 136, with hospital bed expenses

accounting for 86%, home nursing visits for 3%, and enoxaparin drug expenses for 11%.

Direct financial comparisons between the IVUH and LMWH cohorts are skewed by the longer duration of warfarin therapy in the LMWH group (4.4 versus 3.3 days), reflecting the less frequent use of loading warfarin doses in the later time period. To provide a direct measure of cost differences between the 2 strategies, we calculated costs that would have been incurred for each patient in the LMWH group had bridging IVUH instead been used. Within the LMWH cohort, LMWH therapy was associated with a net cost savings of \$865 per patient. Savings were entirely accrued from the subset of patients discharged while still receiving LMWH. A subgroup analysis showed that in the 9 LMWH patients who completed transition to warfarin in the hospital, treatment costs were increased by the LMWH strategy by a mean of \$115 per patient. In the 15 LMWH patients who completed transition to warfarin after discharge, treatment costs were reduced by the LMWH strategy by a mean of \$2197 per patient.

Had a more conservative strategy been followed of requiring a minimum overlap of 5 days of heparin and warfarin during bridging anticoagulation, 10 patients would have needed a combined additional 13 days of hospitalization in the IVUH group, and 16 patients would have needed a combined additional 31 days of treatment in the LMWH group. In this scenario, the LMWH strategy would have been associated with a net savings of \$1654 per patient.

Discussion

The safety findings of this exploratory study of LMWH as bridging anticoagulant therapy in subacute cerebrovascular

disease are encouraging. Patients receiving LMWH generally fared well, with no occurrences of cerebral hemorrhage or major systemic hemorrhage and with significantly fewer incidents of neurological worsening than in a comparison IVUH cohort. This study also establishes feasibility of home administration of high-dose subcutaneous LMWH in recent cerebral ischemia patients.

Limitations to this study include a difference in technique of monitoring adverse events between the IVUH and LMWH groups. All patients in the IVUH group were hospitalized throughout their treatment course and therefore were monitored more closely than the subset of LMWH patients who completed their treatment at home. Patients sent home on LMWH, for example, were not monitored as closely for thrombocytopenia or guaiac-positive stools. More generally, the historical control design of this study leaves it potentially vulnerable to investigator bias and raises the possibility that differences in treatment groups were due to temporal changes in stroke care that occurred between the 2 study periods other than the choice of bridging anticoagulant.

The IVUH cohort frequently exhibited PTT ratios outside the narrow target therapeutic range, but this experience with “intuitive” dosing of heparin in stroke patients agrees with earlier series examining acute heparin anticoagulation in nonstroke and mixed patient cohorts.^{36–38} In our study a therapeutic PTT was achieved 37% of the time. Studies have shown that achievement of target levels of heparin therapy improves modestly when weight-based algorithms are used to determine dosing. Even with preset algorithms, however, underanticoagulation and overanticoagulation are frequent. For example, algorithm-treated groups achieved target PTT ratios only 42% of the time in the study of Rivey and Peterson³⁶ and only 37% of the time in the study of Hollingsworth and colleagues.³⁷

The clinical consequences of failing to maintain a therapeutic PTT are uncertain, but prior studies have suggested that the risk of hemorrhagic transformation of cerebral infarct increases when PTT ratios exceed target range²⁰ and that the risk of progression of thromboembolic disease increases when PTT ratios fail to reach the target range.³⁹

The IVUH cohort experienced significantly more complications than the LMWH cohort. Phlebitis at the intravenous line site occurred in 8%, requiring antibiotic therapy in all. Thrombocytopenia, a well-recognized complication of unfractionated heparin therapy, was noted in 8% of patients. In prior large series of heparin-treated patients, thrombocytopenia has been reported with frequencies ranging from 1% to 26% (most often 5% to 10%). While most often asymptomatic, thrombocytopenia may be associated with a prothrombotic state, contributing to venous or arterial thrombosis through development of antibodies to a complex of heparin with platelet factor 4.⁴⁰ The incidence of thrombocytopenia is reduced in patients treated with LMWH as opposed to IVUH.²²

An additional, underappreciated advantage of transitional LMWH among stroke patients is the release from constraint it imposes on rehabilitation therapy. Current national guidelines call for initiation of physical and occupational therapy as soon as it is medically feasible in patients hospitalized for acute stroke.⁴¹ The presence of an intravenous line, pole, and pump limits a patient’s abilities to ambulate and perform

upper extremity movements during therapy sessions while IVUH is being administered. In our enoxaparin cohort, the use of the LMWH strategy permitted the start of unconstrained rehabilitation therapy an average of 2 days earlier among patients requiring physical and occupational sessions.

In addition to showing a favorable safety and effectiveness profile, the strategy of bridging LMWH substantially decreased length of hospital stay and cost of care compared with bridging IVUH. More than half of patients treated with LMWH completed their bridging therapy at home, and more than half of patients treated with IVUH had their acute hospital stays extended solely to continue to receive intravenous heparin until warfarin reached the therapeutic range. The mean per case savings associated with a bridging LMWH strategy was \$865. This amount represents 15% of the entire current Medicare reimbursement for acute hospital care for ischemic stroke diagnosis related group 14 (\$5800). The chief source of savings was costs of in-hospital days avoided, while increased costs of drug were modest and savings from PTT tests avoided were negligible.

In addition to total costs, an additional important factor in deciding among transitional anticoagulation strategies is whether particular costs are covered by third party payors. For example, currently in the United States, Medicare often does not cover the costs of outpatient LMWH. In such cases, the patient may actually incur greater out-of-pocket costs for a LMWH strategy even when the total healthcare costs of this strategy are less than an IVUH strategy. For most of the patients in our LMWH cohort, we were able to arrange for third party payor coverage of outpatient enoxaparin.

It should be emphasized that the total cost savings in our patients were accumulated despite an aggressive approach to shortening the duration of transitional anticoagulation therapy among these patients. LMWH or IVUH was discontinued generally when the INR reached ≥ 1.8 , rather than waiting for an INR ≥ 2.0 . Warfarin was usually initiated with a loading dose and often on the same day as start of IVUH or LMWH. It is likely that in community practice, savings achievable from a strategy of bridging LMWH are even greater. In addition, recent studies of coagulation physiology and clinical trials of differing warfarin dosing regimens suggest that a regimen of warfarin initiation at a nonloading dose of 5 mg with a fixed 5-day duration of overlap of heparin and warfarin is optimal in patients transitioning to long-term anticoagulation.^{35,42–44}

This study provides preliminary evidence that using LMWH for bridging anticoagulation therapy to warfarin in patients with cerebral ischemia is feasible, potentially safer and more effective than IVUH, and less costly than IVUH. These observations should be confirmed in a prospective, randomized, controlled, double-blind clinical trial comparing bridging regimens such as IVUH, LMWH, and aspirin in patients with stroke subtypes for which there is clear evidence that long-term anticoagulation is indicated.

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