Review
Arterial indications for the low molecular weight heparins
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Abstract

Antithrombotic treatment is of proven importance in patients with acute coronary syndromes. There is now accumulating evidence from several clinical trials in patients with unstable angina pectoris that the low molecular weight heparins (LMWHs) are at least as effective as unfractionated heparin. The LMWHs are easier to use, with the potential to facilitate long-term outpatient treatment. The results of the trials have actually failed to show any clear advantage, however, of the LMWHs over the standard antiplatelet treatment, despite the evidence of a sustained hypercoagulability. Potentially, the use of higher doses of LMWHs could improve the outcomes, but this is as yet unproven and could be associated with unacceptably increased risk of bleeding. During the acute phase of a stroke, aspirin is the first choice of antithrombotic drug because it reduces the risk of recurrent stroke. LMWH cannot be recommended as an antithrombotic agent for the acute treatment of stroke. Prophylactic use of low dose LMWH for the prevention of venous thromboembolism should be considered in every patient with a stroke.

Keywords acute coronary syndrome, low molecular weight heparin, stroke, treatment

LMWHs in the treatment of acute coronary syndromes

The rupture of an atherosclerotic plaque is the main pathophysiologic mechanism underlying acute coronary syndromes [1]. Fissuring plaques expose the flowing blood to subendothelial tissues, and potent stimuli then trigger platelet aggregation, which is followed by the generation of thrombin [2]. Thrombin catalyzes the conversion of fibrinogen to fibrin, is a potent activator of platelet function, and also acts as a vasoconstrictor [2,3]. Both platelet aggregation and thrombin generation require an immediate antithrombotic approach to prevent mortality. The Fifth Consensus Conference on Antithrombotic Therapy guidelines [4] still recommend 160–325 mg aspirin as the antiplatelet of choice for all patients presenting with unstable coronary artery disease, and ticlopidine or clopidogrel as possible alternatives in unstable angina patients.

In four randomized trials comparing aspirin with placebo in unstable angina [5–8], the risk of death or myocardial infarction (MI) was reduced by at least 50% with the regular use of the antiplatelet agent. Aspirin has also been shown to reduce vascular mortality (related to coronary artery, cerebral, or peripheral vascular diseases) and non-fatal reinfarction in the acute phase of MI [9], as well as long term in post-MI patients [10].

The glycoprotein IIb/IIIa receptor inhibitors have been shown to improve the outcomes in patients with unstable angina [11], and are playing an important role in the treatment of acute coronary syndromes. The inhibitors are currently recommended for prevention of restenosis in patients undergoing percutaneous transluminal coronary angioplasty and for patients presenting with severe unstable angina [4]. Since thrombin generation is key in the pathogenesis of thrombosis, additional antithrombotic treatment is necessary to manage

Table 1

Comparison between heparin and low molecular weight heparin (LMWH) size and anticoagulant activity

	Heparin	LMWH
Mean molecular weight	12,000–15,000	4000–6500
Saccharide units (mean)	40–50	13–22
Anti-Xa : anti-IIa activity	1:1	2:1–4:1

Table 2

Comparison of pharmacokinetic properties of heparin and low molecular weight heparin (LMWH)

	Heparin	LMWH
Bioavailability at low doses (%)	30	90
Bioavailability at high doses (%)	90	90
Elimination		
Low doses	Cellular uptake (saturable)	Renal (non-saturable)
High doses	Renal	Renal
Half-life	Dose dependent (30 min–4 h)	Dose independent (2–4 h)

Table 3

The anticoagulant profiles, molecular weights, and plasma half-lives of the commercial low molecular weight heparins discussed

Agent	Anti-Xa : anti-IIa ratio	Molecular weight (saccharide units)	Plasma half-life (min)
Enoxaparin	2.7:1	4500	120–180
Dalteparin	2.0:1	5000	119–139
Nadroparin	3.2:1	4500	132–162

LMWHs (on average, one-third the molecular size of standard heparin) offer a number of pharmacokinetic and pharmacodynamic advantages over heparin (Tables 1 and 2). Their antithrombotic response is more predictable and, as a consequence, laboratory monitoring of therapy is not required [17]. In addition to good bioavailability following subcutaneous injections, LMWHs also have much longer half-lives than unfractionated heparin [18]. These advantages mean that an adequate and persistent anticoagulant effect can be achieved with LMWHs administered by once-daily or twice-daily subcutaneous injections at fixed or weight-adjusted doses.

Although the LMWHs in clinical use have many similarities, they also differ from one another in a number of ways (Table 3). They have different molecular weight distribution profiles, small differences in their specific activities (anti-Xa : anti-IIa activities), different rates of plasma clearance, and some differences in their recommended dosage regimens [17]. The potential advantages over unfractionated heparin, and the positive results of the clinical studies using LMWH in the prevention and treatment of venous thromboembolism have led to the evaluation of these newer compounds in all these clinical settings. Large-scale clinical trials have recently been carried out to evaluate LMWHs (in particular, nadroparin, dalteparin and enoxaparin) in the clinical setting of unstable angina and non-Q-wave MI.

Clinical trials assessing LMWHs in unstable angina and non-Q-wave MI
Nadroparin
The first comparison between a LMWH and unfractionated heparin in patients with unstable angina was in a small study published in 1995 by Gurfinkel *et al* [19] (Table 4). It was a single blind trial in which 211 patients were randomized to twice-daily treatment with either weight-adjusted nadroparin (214 UIC/kg anti-Xa) and aspirin (200 mg/day), intravenous standard heparin (adjusted for the activated partial thromboplastin time) and aspirin, or aspirin alone. Patients with non-Q-wave MI were excluded. After 5–7 days, when the antithrombotic treatment was discontinued, there was a reduction greater than 50% in the rate of recurrent angina, as well as a significant decrease in the rates of silent ischemia

acute coronary ischemia. Unfractionated heparin is still the standard antithrombotic, recommended to be administered for at least 48 hours, in patients with unstable coronary artery disease. It should be given intravenously with an initial bolus of 75 U/kg followed by a continuous infusion of approximately 1250 U/hour to obtain an activated partial thromboplastin time at 1.5–2.0 times control values [4]. Its efficacy in reducing the rate of mortality and acute MI following an episode of unstable angina, in particular when combined with aspirin, has been conclusively proven by several randomized trials [12].

However, unfractionated heparin has a number of limitations directly related to its pharmacokinetic and pharmacodynamic properties. Its anticoagulant effect is unpredictable and varies considerably among patients [13]. To ensure a more rapid therapeutic response, heparin must therefore be given intravenously. This requires hospitalization and frequent monitoring to optimize its effect [14]. Dose adjustments can be cumbersome and, frequently, heparin dosages are suboptimal. Unfractionated heparin has further effects on hemostasis such as the inhibition of platelet aggregation and the increase in vessel wall permeability, which can significantly enhance its potential to cause bleeding complications [15]. Finally, heparin-induced thrombocytopenia, a complication that can lead to serious consequences and that occurs in as many as 3% of treated patients, should always be taken into account for patients treated with unfractionated heparin [16].

Table 4

Randomized trials of low molecular weight heparin (LMWH) in unstable angina and non-Q-wave myocardial infarction (MI)

Study	LMWH	n	Primary outcome	Treatment duration (days)	Follow-up (days)	LMWH (%)	Control (%)	P
Gurfinkel et al, 1995 [19]	Nadroparin	211	MI, death, recurrent angina, urgent revascularization, major bleeding	5–7	5–7	22	59* 63†	0.00001 0.00001
FRISC, 1996 [20]	Dalteparin	1506	MI – death	35–45	6 40 150	1.8 8.0 14	4.8‡ 10.7‡ 15.5‡	0.001 0.07 0.41
FRIC, 1997 [23]	Dalteparin	1506	MI/death/recurrent angina	6	6 45	9.3 12.3	7.6† 12.3‡	0.33 0.96
ESSENCE, 1997 [24]	Enoxaparin	3171	MI/death/recurrent angina	2–8	14 30	16.6 19.8	19.8† 23.3†	0.02 0.02
FRAXIS, 1999 [28]	Nadroparin	3468	MI/death/refractory angina	6 or 14	6/14 days 6 14 90	13.8/15.8 17.8/20.0 22.3/25.2	14.9† 18.1† 22.2†	ns ns ns
FRISC II, 1999 [26]	Dalteparin	2267	Death – MI	90	30 90	3.1 6.7	5.9‡ 8.0‡	0.002 0.17
TIMI 11b, 1999 [27]	Enoxaparin	3910	Death/MI/urgent revascularization	8 or 43	14 43	14.2 17.3	16.6† 19.6†	0.03 0.049

ns, Not significant. * Aspirin, † heparin, ‡ placebo.

and the need for revascularization in the group receiving nadroparin, as compared with the other two groups. The major bleeding rate was comparable between the LMWH and unfractionated heparin. Minor bleedings during the acute phase were significantly less with nadroparin as compared with unfractionated heparin.

Dalteparin

The second LMWH to be tested in this setting was dalteparin. The Fragmin During Instability in Coronary Artery Disease (FRISC) study [20] (Table 4) was a double blind, randomized trial that compared dalteparin (120 IU/kg, twice daily for the first 6 days) and aspirin (75 mg/day) with aspirin alone in 1506 patients. After 6 days of treatment, patients initially randomized to the LMWH were switched to a single, lower, fixed dose (7500 IU) to be continued for up to 45 days. This was the first attempt to reduce long-term ischemic events with an antithrombotic agent. The rationale was based on the observation that, in unstable coronary artery diseases, a persistent hypercoagulable state is present for several months after the acute event [21,22]. Moreover, a raised event rate for at least 6–12 weeks after the acute episode was clinically observed [8]. During the first 6 days of treatment, dalteparin reduced the risk of death or MI in unstable angina patients with a reduction in relative risk of 63%. The frequency of death or MI after 40 and 150 days, the secondary endpoints of the study, did not statistically differ from that of the aspirin alone group.

A second trial with dalteparin was the Fragmin in Unstable Coronary Artery Disease (FRIC) study [23] (Table 4), which was designed in two phases. During the acute phase, 1482 patients received, in an unblinded fashion, the LMWH (120 IU/kg twice daily) or intravenous unfractionated heparin at the common doses (intravenous 5000 IU bolus followed by continuous infusion aimed to achieve a target aPTT of 2.0) with aspirin. The two compounds were found to be equivalent both in efficacy and safety. The second phase was double blinded, and patients were randomized to continue antithrombotic treatment with one, daily fixed dose of dalteparin (7500 IU) or with placebo for up to 45 days from the inclusion in the study. As in the FRISC study, the prolonged treatment with dalteparin did not confer any additional benefit over aspirin alone. In both studies, major bleeding rates were comparable between dalteparin and unfractionated heparin (FRIC) and between dalteparin and placebo (FRISC) during the acute phase, as well as during the prolonged treatment phase.

Latest trials

A new LMWH, enoxaparin, then appeared in the contest. The Efficacy and Safety of Subcutaneous Enoxaparin in non-Q-wave Coronary Events (ESSENCE) trial, with 3171 patients with unstable angina and non-Q-wave MI enrolled, is the largest trial so far conducted [24] (Table 4). It was designed to compare a fixed dose of subcutaneous enoxaparin (1.0 mg/kg twice daily) plus aspirin (100–325 mg/day) with intravenous unfractionated heparin adjusted to the activated

partial thromboplastin time plus aspirin. Antithrombotic treatment was administered for up to 8 days and for a median of 2.8 days. At 14 days, the primary endpoint of the study, the composite risk of death, MI or recurrent angina was significantly lower in patients assigned to enoxaparin than in those receiving unfractionated heparin, with a 16.2% reduction in risk. This reduction was maintained at 30 days. Major bleeding rates were comparable between enoxaparin and unfractionated heparin, whereas the rate of minor bleeding was significantly increased in the enoxaparin group as compared with heparin. At 1 year, the early benefits of enoxaparin over unfractionated heparin in the primary endpoint were still sustained [25]. Nevertheless, even in the enoxaparin group, the primary endpoint was doubled from 16.6% after 14 days to 32.0% after 1 year, thus confirming the need for an improved antithrombotic strategy in the long term.

The FRISC II study specifically addressed the question on the benefits of the long-term treatment, evaluating dalteparin in patients with unstable coronary disease [26] (Table 4). All patients received at least 5 days of treatment with dalteparin (120 IU/kg twice daily) and were then randomized to placebo, or to continue dalteparin, for a total of 3 months (5000 or 7500 IU, according to body weight, twice daily). Aspirin was prescribed to all patients. Once more, the results obtained with the long-term treatment were somewhat unsatisfactory. There was a reduction in the risk of death, MI, and revascularization at 30 days, and a non-significant decrease in the composite endpoint of death or MI at 3 months, but no benefits at all at 6 months. During the extended treatment period, both major and minor bleeding episodes were increased in the dalteparin group.

Following the convincing results obtained in the acute phase, enoxaparin was then evaluated in the long-term treatment. Patients in the Thrombolysis in Myocardial Infarction (TIMI) 11b trial [27] (Table 4) were randomized to unfractionated heparin administered for a minimum of 72 hours, or to therapeutic doses of the LMWH (initially a 30 mg bolus, followed by 1.0 mg/kg every 12 hours) given for up to 8 days and followed by a once-daily fixed dose (40–60 mg twice daily) for an additional 35 days. Almost 4000 patients were included in the trial. As in the ESSENCE trial, at 14 days, the primary endpoint of death, MI, and the need for revascularization were significantly reduced by enoxaparin with a relative risk reduction of 15%. At 43 days the early benefit was significantly maintained (relative risk reduction, 12%), but no additional benefit was produced. As regards safety, there was no difference in major bleeding events during the acute phase, but there was a significant increase in the long-term phase when enoxaparin was compared with placebo.

Finally, the Fraxiparine in Ischaemic Syndrome (FRAXIS) study [28] (Table 4) was the first large trial to assess nadroparin in patients with unstable angina after the results of the study by Gurfinkel *et al*. Standard therapeutic doses of unfractionated heparin administered for 6 days were compared with either 6 or 14 days of nadroparin (100 anti-Xa U/kg bolus followed by 100 anti-Xa U/kg twice daily). The study enrolled 3468 patients, all of whom received aspirin concomitantly. The triple, primary endpoints of death, MI, and refractory angina were not different among the three groups after 6 and 14 days, but were significantly worse at 3 months in the group treated with nadroparin for 14 days. Major bleeding rates were also increased in this group at 14 days as well as at 3 months.

Clinical trials assessing LMWH in acute MI

Among studies that evaluated the use of antithrombotics in patients with acute MI, two were designed to evaluate LMWH: the Fragmin in Acute Myocardial Infarction (FRAMI) study [29], and a study by Glick *et al* [30]. The FRAMI study [29] was a randomized, double blind trial of 776 patients comparing weight-adjusted subcutaneous dalteparin administered twice daily against placebo. Treatment was given for up to 11 days, together with aspirin and streptokinase in the acute phase. After 3 months, the rate of left ventricular thrombi was significantly lower in the LMWH group, as well as the combined rate of left ventricular thrombosis and arterial embolism. There was also a non-significant trend in favor of dalteparin in the reinfarction rate, but the occurrence of both major and minor bleedings was significantly higher.

In the study by Glick *et al* [30], the use of the LMWH was different. The authors randomized 103 patients to a prophylactic dose of enoxaparin (40 mg daily), or to no treatment, for 25 days in an unblinded study. In the acute phase, all patients received streptokinase, unfractionated heparin, and aspirin. After 6 months, there was a significantly lower reinfarction rate and a trend toward a lower angina rate in favor of enoxaparin. No major bleedings were observed and minor bleedings were only detected in the no treatment group.

Persisting dilemmas

There is now accumulating evidence from the results of the recent clinical trials to affirm that the LMWHs are at least as effective as the standard treatment (unfractionated heparin). As a consequence, clinical guidelines [31,32] recommend the use of all LMWHs as a class. Following the data of the ESSENCE trial and of the TIMI 11b trial, enoxaparin was the only LMWH to show superiority over unfractionated heparin. In all settings, the different biochemical properties of the compounds have always required individual tests before any potential approval for clinical use, but how this difference can be determined on such results is not clear. Differences in study designs or the 'play of chance' have been proposed. Differences in the quality of the management of intravenous unfractionated heparin therapy among centers have also been observed. This is a reminder of how problematic it can be to obtain good quality unfractionated heparin dose-adjusted therapy in the routine clinical practice of an average hospital.

As in the case of venous thromboembolism, it is likely that unfractionated heparin and LMWH are, at the end, substantially equivalent. This equivalence can be extended to all different LMWH. The LMWHs, however, have the advantage of easier use. The results of specifically addressed trials have so far actually failed to show any clear advantage of the LMWHs over the standard antiplatelet treatment, despite the evidence of a sustained hypercoagulability. The use of higher doses might improve the outcomes, but the consequent increased risk of bleeding is a high price to pay.

Finally, potential markers of a poor outcome to identify subgroups of patients most likely to benefit from the long-term therapy would be of great help. From a substudy of the FRISC trial, a statistically significant protective effect of dalteparin, during the long-term treatment phase, was found in the subgroup of patients with troponin T levels ≥0.1 µg/l (event rate reduced from 14.2% with placebo to 7.4% with dalteparin), whereas patients with troponin T levels <0.1 µg/l did not benefit from the therapy with the LMWH [33]. The troponin-T-negative patients showed a lower rate of adverse events independent of the treatment received (4.7% with placebo and 5.7% with dalteparin). This suggests that troponin T levels measured on admission could identify patients at higher risk for whom the prolonged treatment might be beneficial. Also, another substudy from the ESSENCE trial [34] identified Von Willebrand factor, a phase-reactant protein, as a possible independent predictor of the severity of the disease that could be useful to determine a more appropriate treatment strategy.

LMWHs in the treatment of acute stroke

Ischemic stroke, although heterogeneous in nature, shares a pathophysiological basis that is similar to the underlying mechanisms of acute coronary syndromes. While established methods for prevention of ischemic stroke exist – treatment with antiplatelets, oral anticoagulants or carotid endarterectomy [35] – there is no established specific anticoagulant treatment for acute episodes that has shown reduction in mortality or improvement in functional status [36,37]. Anticoagulant agents, including heparin, have been given for decades, but their benefits are unproven and their use therefore remains controversial [38–40]. If anticoagulants are used in patients with stroke, there is the worry of increasing the likelihood of intracranial hemorrhage, thereby worsening the prognosis. Data from the large, randomized International Stroke Trial showed that there was a significantly increased risk of both intracranial and extracranial hemorrhage with unfractionated heparin, even when given at low doses (5000 IU subcutaneously twice daily) [41]. LWMH with less potential for hemorrhage would, in theory, have some advantages for the treatment of stroke, and for the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Finally, in the National Institute of Neurological Disorders and Stroke (NINDS) Recombinant Tissue Plasminogen Activator

Stroke Study, a statistically and clinically significant improvement in functional outcome was found when using thrombolytic therapy in patients with acute stroke who presented within a narrow time window of 3 hours after the start of symptoms [42,43].

Clinical trials assessing LMWH in patients with acute stroke

The Hong Kong Fraxiparine in Stroke Study (FISS) was the first investigation comparing nadroparin in a low dose (4100 IU once daily) or a high dose (4100 IU twice daily; comparable with doses used in patients with DVT) for a period of 10 days versus placebo [44]. Patients with acute ischemic strokes of all degrees of severity, within 48 hours of the onset of symptoms, were included. The primary endpoint consisted of 'poor outcome', which was defined as death or dependency with respect to daily activities during the 6 months after randomization. This endpoint was reached in 45% of patients in the high dose LMWH group, 52% in the low dose LMWH group, and 65% in the placebo group. There was a highly significant dose-dependent effect among the three study groups in favor of the LMWH ($P < 0.005$ by chi-square test for trend). In this study, there was no significant difference between the treated patients and those patients given placebo in rates of hemorrhagic transformation of the infarct. After this positive outcome of the FISS, several other studies have been performed, including the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) [45] and the Fraxiparine in Stroke Trial (FISS bis) [46].

In the recent Heparin in Acute Embolic Stroke Trial (HAEST) [47], LMWH was compared with aspirin. The HAEST has compared the effect of the LMWH dalteparin (100 IU twice a day) versus that of aspirin (160 mg per day), over 14 days, in patients with atrial fibrillation who suffered an acute ischemic stroke within 30 hours of onset. The primary endpoint in this study was recurrent stroke during the first 14 days. The data, however, did not show a benefit of the LMWH with regard to this endpoint.

The overall conclusion from these three studies is that none has been able to reduplicate the benefit seen in the FISS on the overall outcome of patients with acute ischemic stroke. Clinicians may still want to use heparin for prevention of DVT and PE, for which patients with stroke are at high risk. Systemic reviews have clearly demonstrated that anticoagulant therapy significantly reduced the risk for DVT from 44 to 10% (odds reduction, 80%) [48]. There was also a significant reduction in the odds of PE with anticoagulants but, as the authors noted, the absolute benefit was rather small with only four PEs avoided per 1000 patients treated [48]. In view of these data, the use of low dose LMWH could be considered in a patient with an acute stroke.

commentary

review

research

Conclusions

The authors conclude that, for the acute phase of a stroke, aspirin is the first choice of antithrombotic drug because it reduces the risk of recurrent stroke. LMWH cannot be recommended as an antithrombotic agent for the acute treatment of stroke. Prophylactic use of low dose LMWH for the prevention of venous thromboembolism could be considered in every patient. Finally, long-term oral anticoagulant treatment should be given to patients with atrial fibrillation after stroke or transient ischaemic attack (target range International Normalized Ratio, 2.0–3.0) but the time to start this medication is as yet uncertain.

Competing interests

None declared.

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