

Theme Issue Article

M118 – A rationally engineered low-molecular-weight heparin designed specifically for the treatment of acute coronary syndromes

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Summary

The initial choice of anticoagulant therapy administered in emergency departments for acute coronary syndromes (ACS) has important consequences for subsequent patient care, as neither unfractionated heparin (UFH) nor low-molecular-weight heparin (LMWH) are ideally suited for all potential clinical treatment pathways. UFH remains widely used for surgical interventions because of the ability to rapidly reverse its anticoagulant activity. However, the unpredictable pharmacokinetic profile of UFH presents safety issues, and the low subcutaneous bioavailability limits the utility of UFH for patients who are medically managed. LMWH has superior pharmacokinetic properties, but its anticoagulant activity cannot be effectively monitored or reversed during surgery. There is an unmet medical need for a baseline anticoagulant therapy that addresses these

shortcomings while retaining the beneficial properties of both UFH and LMWH. We describe here M118, a novel LMWH designed specifically for use in the treatment of ACS. M118 shows broad anticoagulant activity, including potent activity against both factor Xa (~240 IU/mg) and thrombin (factor IIa; ~170 IU/mg), low polydispersity, high (78%) subcutaneous bioavailability in rabbits, and predictable subcutaneous and intravenous pharmacokinetics. Additionally, the anticoagulant activity of M118 is monitorable by standard coagulation assays and is reversible with protamine. M118 demonstrates superior activity to conventional LMWH in a rabbit model of abdominal arterial thrombosis without increasing bleeding risk, and is currently being evaluated in a phase II clinical trial evaluating efficacy and safety in patients undergoing percutaneous coronary intervention.

Keywords

Heparins, coagulation inhibitors, acute myocardial infarction, arterial thrombosis, thrombin

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Introduction

Arterial thrombosis associated with acute coronary syndromes (ACS) is a major cause of patient morbidity and mortality in the Western world. The etiology of arterial thrombosis is distinct from that of venous thrombosis, and requires a different therapeutic approach (1). Acute arterial thrombosis is associated with rupture of atherosclerotic plaques, leading to exposure of sub-endothelial collagen and recruitment of platelets. Anti-thrombin activity is particularly important in the arterial setting due to the high degree of platelet involvement (2). Thrombin activates platelets through the thrombin receptor. Furthermore, activated platelets have been shown to be the primary surface on which

thrombin is generated, thus setting up a feedback loop that leads to rapid thrombus formation (3, 4).

Thrombin (factor IIa) inhibition by heparin requires a polysaccharide chain of a minimum of 18 saccharide units or ~5,300 Daltons (5). While unfractionated heparin (UFH; average MW ~15,000 Daltons) has potent anti-thrombin activity, low-molecular-weight heparins (LMWHs; average MW ~4,500 Daltons) have comparably low anti-thrombin activity (6, 7). Enoxaparin, the most widely used LMWH, has an anti-factor Xa:IIa ratio of ~4:1 compared to ~1:1 for that of UFH. The difference in the anti-thrombin activity of UFH and LMWHs is further exacerbated *in vivo*. The longer chains of LMWH, which contain both anti-factor Xa and anti-factor IIa activity, are cleared faster than

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the smaller chains that contain only anti-factor Xa activity. Thus over time, the in-vivo anti-factor Xa:IIa ratio of LMWH increases from ~4:1 to ~14:1 (8).

Patients that present to an emergency department with signs and symptoms consistent with myocardial infarction are likely to already have an existing and evolving thrombin-rich clot. The initial choice of anticoagulation therapy has potentially profound consequences on the outcome during subsequent stages of patient management (9). However, the exact treatment pathway, such as medical management versus percutaneous coronary intervention (PCI), may not be known at the time of presentation. Patients who require immediate interventional surgery may be given UFH, because its anticoagulant activity, unlike that of LMWH, can be fully reversed during surgery with protamine (10). In contrast, medically-managed ACS patients may be started on LMWH because of its superior subcutaneous bioavailability and more predictable pharmacokinetic properties compared to that of UFH. However, many ACS patients who are started on LMWH in the emergency department, may need to be switched to UFH prior to an unscheduled interventional or surgical procedure. UFH and LMWH have very different pharmacokinetic profiles, making it difficult to transition from one therapy to the other and resulting in the potential for under- or over-dosing. Dosing is further complicated by the fact that the residual anticoagulant level of the LMWH cannot be readily measured in the hospital setting. Clinical trials have demonstrated that patients who are switched from LMWH to UFH experience worse treatment outcomes than patients who are started and maintained on UFH (11). Consequently, the ideal anticoagulant used initially in the emergency department would be one that can be utilised for all patients, regardless of the potential need for subsequent procedural intervention (1, 9, 12).

In this manuscript, we describe M118, a rationally engineered heparin derivative that is specifically designed to incorporate the optimal properties necessary to address the anticoagulation needs of both ACS patients that are medically managed as well as patients that require interventional procedures.

Materials and methods

M118

M118 is a LMWH derived from porcine intestinal mucosa. M118 has a structural formula of $C_{12m}H_{14m+1}O_{10m}N_mNa_mR_{3m-1}R1_m$, $C_{12m}H_{14m+2}O_{10m+1}N_mNa_mR_{3m}R1_m$, where $n =$ average number of disaccharide repeats, $m = 1+n$, R is H or SO_3Na , and R1 is SO_3Na or $COCH_3$ (Fig. 1).

M118 is a complex mixture of polysaccharide chains characterised by a weight averaged molar mass between 5,500 and 9,000 Daltons and a polydispersity of approximately 1.0. On a per mg basis, it has activity of approximately 240 anti-factor Xa and 170 anti-factor IIa IU as measured against the 2nd International Standard of LMWH. M118 is structurally distinct from existing LMWHs as well as UFH. M118 is generated by enzymatic depolymerisation and therefore does not possess unusually modified saccharide structures at the reducing end of chains, as found in LMWHs that are manufactured using a chemical process to depolymerise UFH (13). Furthermore, the pentasaccharide sequence that is essential for binding antithrombin is

enriched during the manufacturing process, resulting in enhanced activity of M118 compared to other LMWHs and UFH.

The manufacture of M118 involves a four-step process.

- 1) Commercially available UFH is subjected to a step-wise series of aqueous precipitations to remove lower-molecular-weight chains. This step also selects material with a higher molar proportion of the region that binds antithrombin, thereby enriching for anticoagulant properties. This material is designated Intermediate 1.
- 2) Intermediate 1 is digested with a proprietary heparinase enzyme (M011) in aqueous buffer to produce Intermediate 2. This step further reduces molecular weight, but due to the specificity of M011 enzyme, does not compromise the ability of the resulting product to bind antithrombin.
- 3) Size exclusion chromatography (SEC) is used to separate components of Intermediate 2 with high anti-factor Xa and anti-factor IIa activity away from the lower-activity materials. The product, designated Intermediate 3, has a greater specific activity against factor Xa than either the UFH starting material or other LMWHs.
- 4) Individual or combined Intermediate 3 materials are dissolved in purified water, filtered through a 0.2 μm filter, and lyophilised to produce M118.

Anti-factor Xa, anti-factor IIa, aPTT, and ACT activity assays

Anti-factor Xa, anti-factor IIa, and aPTT activity assays were performed on an automated coagulation analyser (Stago), as previously described (14). Anti-factor Xa and anti-factor IIa activity was measured using the chromogenic substrates S-2222 and 2238, respectively. The concentration of LMWH in unknown samples was calculated by comparing to the calibration curve derived from the 2nd International Standard for LMWH. Activated clotting time (ACT) was measured with a Hemochron Junior Signature Microcoagulation System, as per manufacturer's directions.

Animal welfare

All of the surgical procedures were terminal and approved by Momenta Pharmaceuticals IACUC (protocol #01-2006), in compliance with the Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals.

Rabbit abdominal arterial thrombosis model

Male New Zealand white rabbits (3–3.5 kg) were obtained from Millbrook (Amherst, MA, USA). The rabbits were anaesthetised with a mixture of ketamine (45 mg/kg) and xylazine (5 mg/kg), and maintained with isoflurane under voluntary ventilation control for the duration of the experiment. Rabbits ($n = 6$ /group) were monitored for heart rate, direct blood pressure, oximetry, respiratory rate, and rectal body temperature. A marginal vein of the ear was cannulated for fluid infusion and intravenous injection of test articles. The carotid artery was catheterised for blood pressure measurement and collection of blood samples.

After cannulation of the carotid artery, a 2.5 cm segment of the abdominal aorta was isolated beginning at the arterial iliac bifurcation. The aorta segment was carefully exposed and all side branches within the 2.5 cm segment were ligated. A 2.5 mm

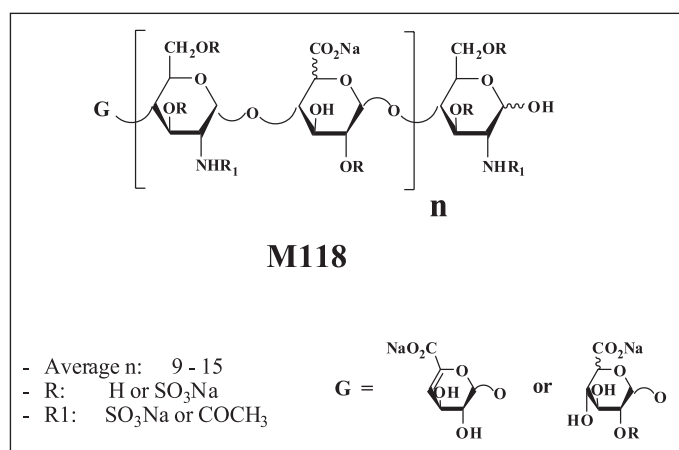


Figure 1: Chemical structure of M118.

ultrasonic flow probe (Transonic Systems) was placed on the proximal portion of the isolated segment. A 2-mm-wide plastic wire tie (Mass Electric Supply) was progressively constricted around the distal end of the aorta segment to reduce blood flow until hyperemia response was abolished without altering base line flow, creating a critical stenosis which is characterised by a reduction of blood vessel diameter of approximately 85%.

To initiate acute thrombosis, the internal section surface of the aorta wall between the constrictor and the flow probe was injured by applying a continuous electrical current of 200 μ A for up to 120 minutes (min) beginning 10 min post intravenous drug infusion. Electrolytic injury was accomplished via a electrode, consisting of a 27-gauge needle bent into a 90 degree angle. The electrode was connected to the positive pole pole of a constant current device and to a cathode connected to a distant subcutaneous site. The electrode was left in place for the entire duration of the experiment. To minimise variability, the same surgeon per-

Table 1: Structural features and activity of M118, enoxaparin, and unfractionated heparin (UFH). * $\Delta\text{UH}_{\text{NAC},65}\text{GH}_{\text{NS},35,65}$ is the structural motif defining the antithrombin binding sequence of heparin. ** Note that M118 and enoxaparin activity are measured in International Units based on an international LMWH reference standard while UFH is measured in USP units. The two units are not directly comparable.

Attribute	M118	Enoxaparin	UFH
$\Delta\text{UH}_{\text{NAC},65}\text{GH}_{\text{NS},35,65}$ (mole %)	~9.4	~4.7	~4.2
Anti-factor Xa activity (IU/mg)	~240**	~100**	~150** (USP U/mg)
Anti-factor IIa activity (IU/mg)	~170**	~25**	~150** (USP U/mg)
Anti-factor Xa:IIa ratio	~1.4	~4	~1
Average molecular weight	~6,500	~4,500	>15,000
Polydispersity	~1.0	~1.3	~1.5

formed all procedures. Test and control articles were administered intravenously after establishing critical stenosis. Aorta baseline blood flow was monitored and recorded continuously throughout the study beginning 20 min prior to stenosis creation and continued for the duration of the study.

Rabbit internal bleeding model

Male New Zealand white rabbits (3–3.5 kg) were anaesthetised and monitored as described above. All rabbits exhibited normal vital signs, with no sign of distress, and survived the entire duration of the experiment. Indwelling catheters were placed in the femoral vein and carotid artery to allow for intravenous administration of fluids and test articles and monitoring of the blood pressure. Seven groups of rabbits ($n = 6/\text{group}$) were administered test compounds or saline for 5 min following injection of the test articles. Two biopsies were performed on the liver and one on the left kidney, using a 6 mm biopsy punch. Each wound was allowed to bleed freely for no longer than 15 seconds, and was covered with an absorbable surgical sponge from 3M #CPD914DD. The laparotomy was then closed for 1 hour (h) and reopened for collection of the absorbable sponges from the biopsy sites. The rabbits were euthanised with Phenobarbital (100 mg/kg intravenous) after the sponges were retrieved. Blood loss was measured by weighing the sponges.

Statistics

Time to occlusion data from the rabbit thrombosis model was evaluated by an unpaired Student's t-test. Percent occlusion data was evaluated by a z-test.

Results and discussion

Design of M118

Sundaram et al. previously demonstrated that LMWHs can be engineered to optimise for specific properties using selective enzymes and novel analytical techniques (14). We have further refined this process to generate M118, a novel LMWH designed to have optimal properties for treatment of ACS. Specifically, M118 was designed to have a high specific activity for both anti-factor Xa and anti-factor IIa activity, low polydispersity to create a molecule with high subcutaneous bioavailability and predictable pharmacokinetic properties, high anti-factor IIa activity to allow monitoring by routinely used point-of-care coagulation assays, and sufficient size and charge density to be reversible by protamine. M118 has an anti-factor Xa activity of ~240 IU/mg and anti-factor IIa activity of ~170 IU/mg (Table 1). In contrast, the most widely used LMWH, enoxaparin, shows lower anti-factor Xa specific activity (~100 IU/mg) and greatly reduced anti-factor IIa activity (~25 IU/mg). Thus, the anti-factor Xa:IIa ratio of M118 (1.4:1) is more similar to that of UFH (1:1) than to enoxaparin (4:1). Selective separation techniques used in the M118 manufacturing process yields a mixture with a polydispersity of approximately 1.0 and an average molecular mass weight of ~6,500 Daltons. In contrast, UFH has a polydispersity of 1.5 and an average molecular weight of ~15,000 Daltons. The high molecular weight and high polydispersity of UFH are thought to contribute to its poor subcutaneous bioavailability and unpredictable pharmacokinetic profile.

Subcutaneous bioavailability and pharmacokinetic profile

One of the limitations of UFH therapy is its poor subcutaneous bioavailability. Thus, UFH is primarily administered intravenously, which limits its use to the hospital setting. M118 showed a subcutaneous bioavailability of 78% in rabbits (Fig. 2A), much greater than that observed for UFH (25%). Following a 1.5 mg/kg subcutaneous dose, M118 exhibited a $T_{1/2}$ of 1.76 ± 0.04 h, a C_{max} of 1.46 ± 0.24 IU/ml, and an AUC of 8.14 ± 1.06 IU*h/ml.

Next enoxaparin and M118 were both dosed at 300 IU/kg subcutaneously (Fig. 2B). Although enoxaparin and M118

showed comparable anti-factor Xa activity over time, the anti-factor IIa activity of enoxaparin was markedly lower than that observed for M118. The in-vivo pharmacodynamic profile of enoxaparin showed that the anti-factor Xa:IIa ratio varies greatly over time (Fig. 2C). The anti-factor Xa:IIa ratio of enoxaparin showed a "U" shaped curve. At early time points, the high anti-factor Xa:IIa ratio of enoxaparin is largely attributed to the faster subcutaneous absorbance of low-molecular-weight chains containing only anti-factor Xa activity compared to that of higher-molecular-weight chains that contain both anti-factor Xa and anti-factor IIa activity. At later time points, the high anti-factor Xa:IIa ratio is attributed to the faster clearance of higher-molec-

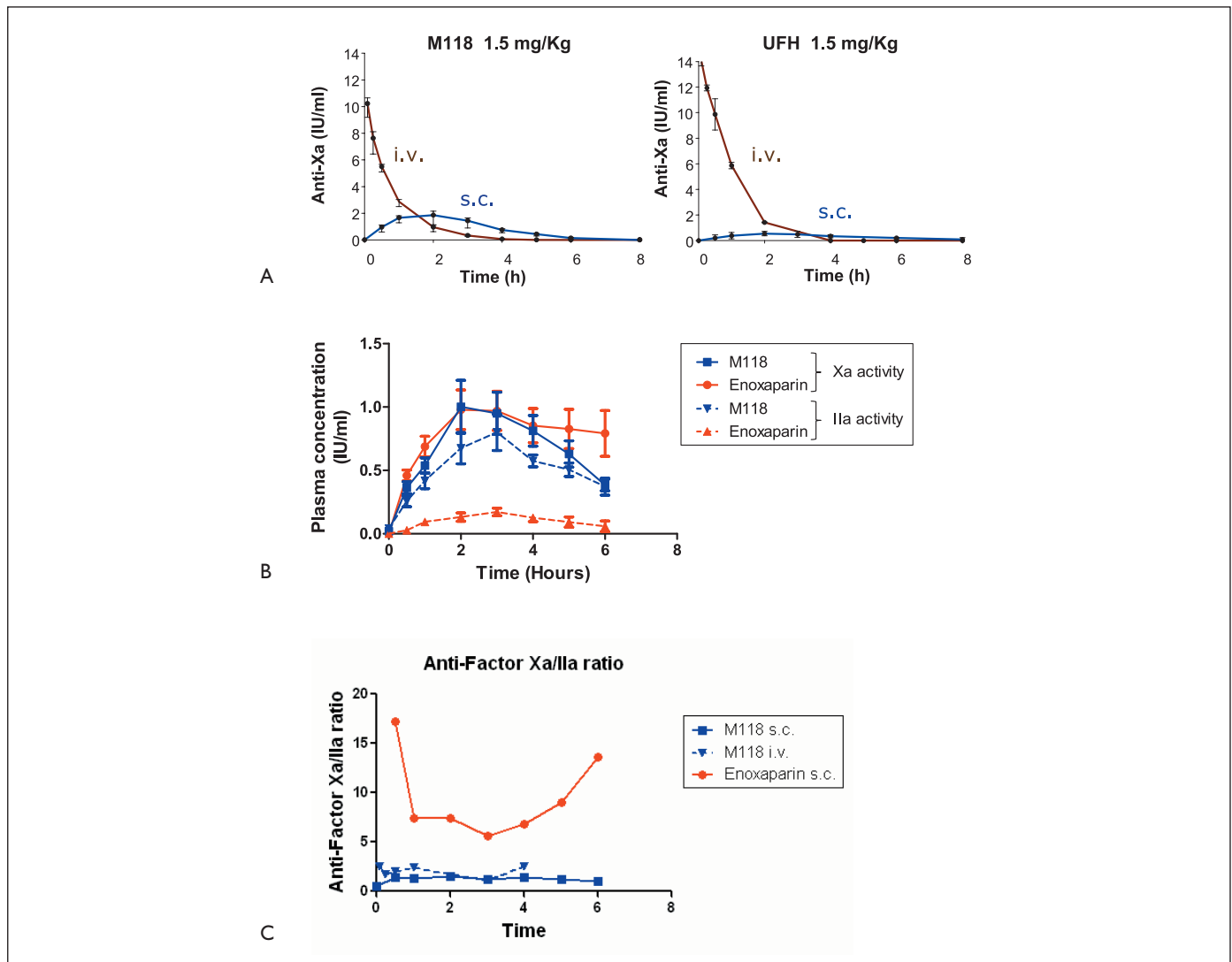


Figure 2: Pharmacokinetic profile of M118. A) Subcutaneous (s.c.; blue line) and intravenous (i.v.; brown line) pharmacokinetic profiles of M118 and unfractionated heparin (UFH). New Zealand white rabbits ($n = 6$ animals/group) were dosed s.c. or i.v. with 1.5 mg/kg of M118 (left panel) or UFH (right panel). Blood was collected at various time points as indicated, and anti-Factor Xa activity was measured with a chromogenic anti-factor Xa activity assay. B) Subcutaneous pharmacokinetic profile of M118 and enoxaparin. New Zealand white rabbits ($n = 6$ animals/group) were dosed s.c. with 300 IU/kg of M118 (blue line) or enoxaparin (red line). Blood was collected at various time points as indicated,

and anti-factor Xa (solid lines) and anti-factor IIa (dashed lines) activity was measured with a chromogenic activity assay. C) In-vivo profile of anti-factor Xa:IIa ratio of M118 and enoxaparin. New Zealand white rabbits were dosed s.c. with 300 IU/kg of M118 (solid blue line) or 300 IU/kg of enoxaparin (solid red line), or i.v. with 360 IU/kg of M118 (dashed blue line). Blood was collected at various time points as indicated, and anti-factor Xa and anti-factor IIa activity was measured using chromogenic anti-factor Xa and anti-factor IIa activity assays. The change in anti-factor Xa:IIa ratio over time is plotted.

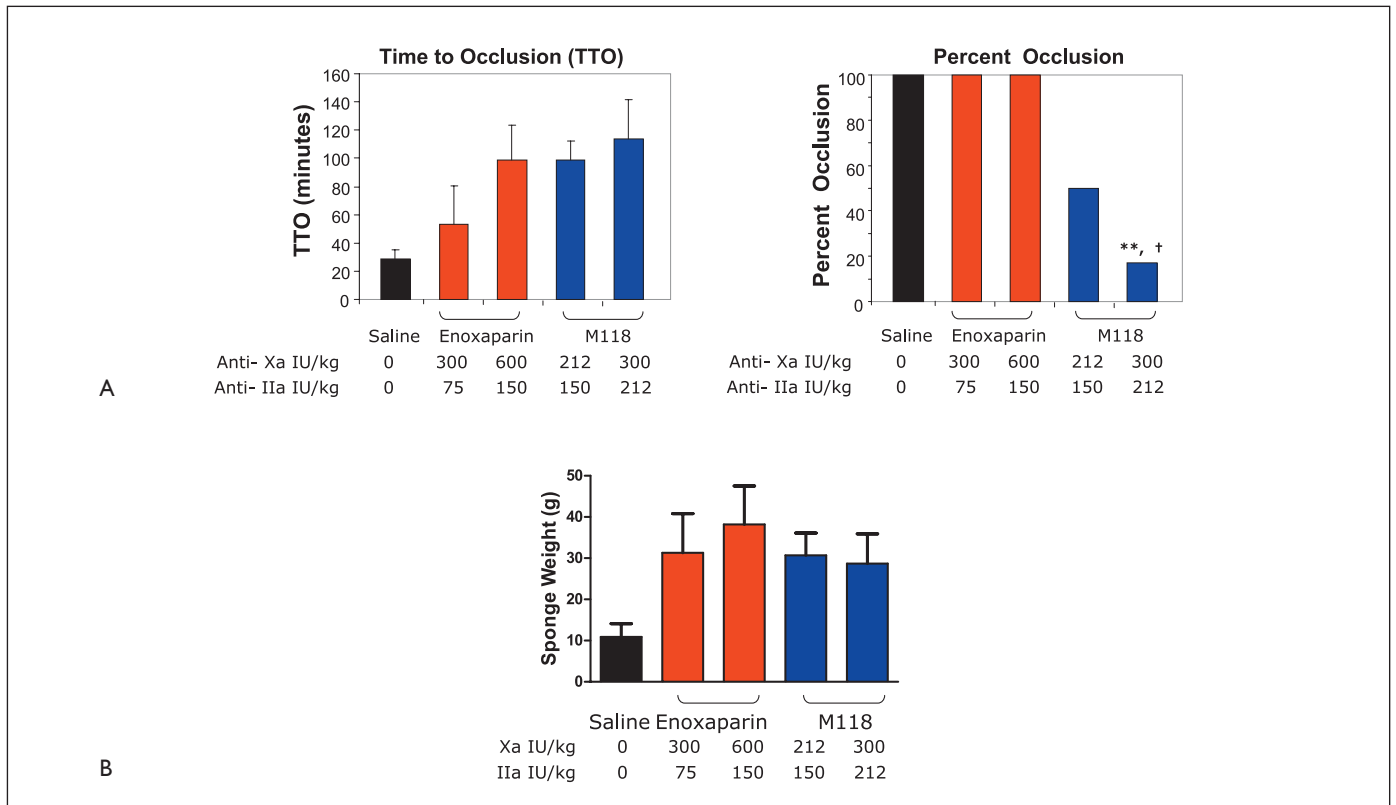


Figure 3: In-vivo efficacy and safety of M118. A) Rabbit abdominal arterial thrombosis model. Acute thrombosis was induced in anesthetized male New Zealand white rabbits (3–3.5 kg) by subjecting the abdominal aorta to a continuous electrical current of 200 μ A for up to 90 minutes. Various doses of M118 (blue) or enoxaparin (red) were administered intravenously (i.v.) prior to electrolytic injury (n = 6 animals/group). Control animals were treated with saline (black). Blood flow was monitored until complete occlusion or up to 120 minutes after establishing baseline blood flow, hyperaemia response, and vitals. Animals that showed no occlusion at the end of the observation period were assigned a value of

120 minutes. B) Internal bleeding model. Anesthetized male New Zealand white rabbits (n = 6 animals/group) were administered M118 (blue), enoxaparin (red) or saline (black) by i.v. injection. Two biopsies were performed on the liver and one on the left kidney, using a 6 mm biopsy punch. Each wound was allowed to bleed freely for no longer than 15 seconds, and then covered with an absorbable surgical sponge. The laparotomy was then closed for 1 hour and reopened for collection of the absorbable sponges from the biopsy sites. Blood loss was measured by weighing the sponges.

ular-weight chains containing both anti-factor Xa and anti-factor IIa activity compared to that of lower-molecular-weight chains that contain only anti-factor Xa activity (8). Thus, the anti-factor Xa:IIa ratio of enoxaparin varies from ~5:1 to over10:1 *in vivo*, indicating that the total anticoagulant activity is not linear with respect to anti-factor Xa activity (Fig. 2C). The unpredictable anti-factor Xa:IIa ratio and the inability to monitor residual anticoagulant activity of conventional LMWH makes it especially challenging to switch patients from LMWH subcutaneous therapy to UFH intravenous therapy in the event of an emergency interventional or surgical procedure.

M118 is manufactured through a process that enriches for heparin chains that contain both anti-factor Xa and anti-factor IIa activity with low polydispersity. Thus the anti-factor Xa:IIa ratio of M118 is low (~1.4:1) and remained constant over time *in vivo* (Fig. 2C). Importantly, the anti-factor Xa:IIa profile for M118 remained the same, whether it was administered by subcutaneous injection or by intravenous injection (Fig. 2C). These results suggest that the pharmacokinetic properties of M118 are

predictable over time, and could allow for seamless switching from M118 subcutaneous therapy to M118 intravenous therapy.

In-vivo efficacy and bleeding risk

The high degree of platelet involvement in arterial thrombosis suggests that anti-factor IIa activity is particularly important for treating ACS. Activated platelets are the major surfaces upon which thrombin is generated (3, 4). Thromboelastograms demonstrate that anti-factor IIa and anti-factor Xa therapeutics operate on different phases of thrombin generation (4, 15). Anti-factor Xa therapeutics delay the onset of thrombin generation but show minimal effect on the absolute amount of thrombin generated, while anti-factor IIa therapeutics reduce the total activity of thrombin generated but do not delay the onset of thrombin generation. UFH, which has both potent anti-factor Xa and anti-factor IIa activity inhibits both the onset and magnitude of thrombin generation, while conventional LMWHs have a greater effect on the onset than the magnitude of thrombin generation. Recent *in-vitro* mechanism studies indicate that M118 behaves more simi-

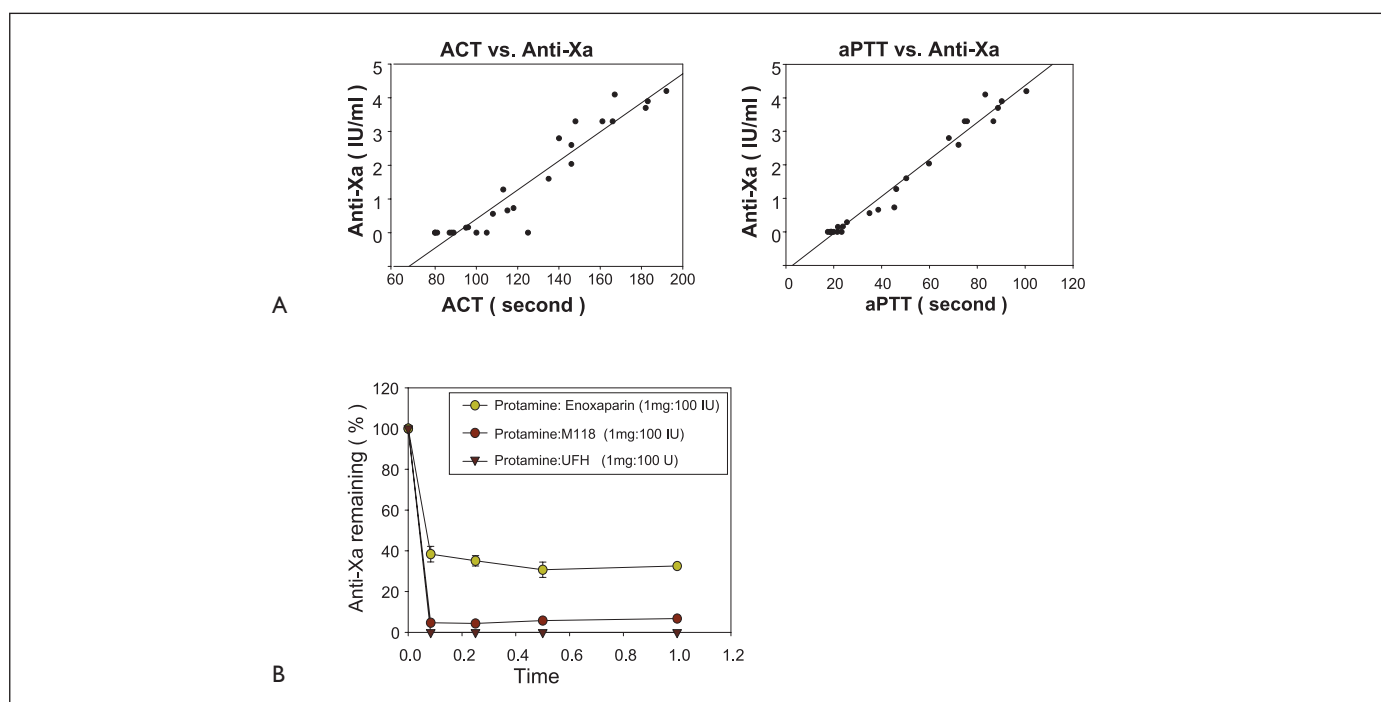


Figure 4: Monitorability and reversibility of M118. A) Correlation of M118 anti-factor Xa activity with aPTT and ACT assays. Anti-factor Xa, aPTT and ACT activity measurements were measured as described in *Methods*. B) Reversibility of anticoagulation activity with protamine. M118 (1 mg/kg), enoxaparin (1 mg/kg) and UFH (100 USP/kg) were intravenously injected into New Zealand Rabbits (n=3 per group). Blood was taken at 3 minutes after injection, and then protamine (1 mg per

100 IU enoxaparin and M118 or 100 USP units (UFH) was infused intravenously via the marginal ear vein at 5 minutes. Additional blood samples were collected at 5, 15, 30 and 60 minutes after the protamine injection. Anti-factor Xa, anti-factor IIa, and aPTT activity were measured on an automated coagulation analyser instrument, and ACT was measured on a Hemocron Jr. Signature instrument.

lar to UFH than enoxaparin in inhibiting both the onset and magnitude of thrombin generation (16).

The contribution of anti-factor IIa activity in arterial thrombosis was investigated in a rabbit model of abdominal arterial thrombosis. Acute thrombosis was induced by continuous electrolytic injury of the abdominal aorta for up to 90 min. Enoxaparin or M118 was administered just prior to injury. If the dose was adjusted based upon equivalent anti-factor Xa activity (~300 IU/kg anti-factor Xa activity), M118 showed superior efficacy to enoxaparin as determined by both time to occlusion (114 ± 14 min vs. 53 ± 27.4 min, $p < 0.05$) and percent occlusion (17% vs. 100%, $p < 0.05$) (Fig. 3A). The determination for time to occlusion (TTO) underestimates the efficacy of M118, as TTO was followed for a maximum of 120 min, and animals that showed no occlusion at this endpoint were assigned a value of 120 min. At 300 IU/kg anti-factor Xa activity, M118 has an anti-factor IIa activity of ~212 IU/kg, while enoxaparin has an anti-factor IIa activity of ~75 IU/kg.

In contrast, if the dose was adjusted based upon equivalent anti-factor IIa activity (150 IU/kg), M118 and enoxaparin showed similar efficacy in prolonging TTO (98 ± 27 min vs. 99 ± 24.2 min; Fig. 3A). However, this activity was achieved by increasing the anti-factor Xa dose of enoxaparin to ~600 IU/kg vs. ~212 IU/kg for M118. These results suggest that enoxaparin can be efficacious in arterial thrombosis only if the dose is increased to compensate for its lower anti-factor IIa activity. It is important

to note that while enoxaparin and M118 show similar efficacy in prolonging TTO at matched anti-factor IIa doses, M118 still showed a trend to superior activity when assessing percent occlusion (50% vs. 100%). In addition, rabbits exhibited transient disruptions in blood flow, as platelet thrombi formed and were subsequently dislodged prior to complete occlusion. Rabbits treated with 600 IU/kg of enoxaparin exhibited 4 ± 1 transient disruptions in blood flow, while rabbits treated with 200 IU/kg of M118 exhibited only 1 ± 1 transient disruptions in blood flow. The superior profile of M118 at matched anti-factor IIa doses, may reflect broader inhibition of coagulation proteases, such as factor IXa and factor XIa, by M118.

The bleeding risk of M118 was assessed in an internal bleeding model in rabbits. Rabbits treated with M118 or enoxaparin were subjected to punch biopsies in the liver and kidney, and blood loss was quantified over 30 min. Rabbits treated with M118 or enoxaparin based on equivalent anti-factor Xa activity (300 IU/kg) showed similar bleeding risk (28.7 ± 7.2 g vs. 31.3 ± 9.5 g blood loss, respectively), despite the superior efficacy and higher anti-factor IIa activity of M118 (Fig. 3B). In contrast, rabbits treated with equivalent anti-factor IIa activity (75 IU/kg) showed a trend towards increased bleeding with enoxaparin than with M118. These results suggest that increasing the enoxaparin dose to achieve therapeutic levels of anti-factor IIa activity may increase the risk of bleeding. Clinical studies have shown that a

high dose of enoxaparin can achieve comparable efficacy to UFH in ACS, but with an increase in bleeding risk (11, 17).

Monitorability and reversibility

The predictable pharmacokinetic profile of M118 is designed to allow M118, like conventional LMWHs, to be used without routine monitoring. However, the ability to monitor and reverse the anticoagulation activity of M118 could provide an important safety advantage over other LMWHs in the event of an emergency surgical procedure or for high-risk patients, such as diabetics with impaired renal function. Routine point-of-care assays to measure coagulation status, such as aPTT and ACT, largely reflect thrombin (factor IIa) activity. Thus, the anticoagulation activity of LMWHs that have low antithrombin activity and an anti-factor Xa:IIa ratio that varies over time *in vivo* cannot be accurately measured by aPTT or ACT. In contrast, M118, which has potent anti-thrombin activity and exhibits a steady anti-factor Xa:IIa ratio over time *in vivo*, showed an excellent correlation of anti-factor Xa activity to aPTT and ACT (Fig. 4A). The ability of protamine to reverse anticoagulant activity is a function of the size and charge density of the individual heparin chains. Conventional LMWHs are too small to be fully reversible with protamine (10). In contrast, the anticoagulant activity of M118 was rapidly reversible *in vivo* to sub-therapeutic levels with protamine (Fig. 4B).

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Conclusion

We have engineered a novel LMWH to specifically address the shortcomings of UFH and conventional LMWH in the treatment of ACS. M118 is designed to be the baseline anticoagulant of choice that can be administered immediately in the emergency department irrespective of the subsequent treatment pathway, thus eliminating potential adverse events associated with switching anticoagulant therapies. The predictable pharmacokinetic profile and subcutaneous bioavailability of M118 is designed to allow for convenient and safe use in patients that are medically managed. The monitorability and reversibility is designed to provide a superior safety advantage over conventional LMWHs for patients with bleeding complications, high-risk patients with renal impairment, or patients requiring percutaneous or surgical intervention. The broad anticoagulant activity, including potent anti-thrombin activity, is designed to provide superior efficacy in an arterial thrombosis setting where there is a high degree of platelet involvement. Currently, M118 is being tested in a Phase II clinical trial for patients undergoing PCI.

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