Interventional Cardiology

Evaluation of a New Heparin Agent in Percutaneous Coronary Intervention

Results of the Phase 2 Evaluation of M118 IN pErcutaNeous Coronary intErvention (EMINENCE) Trial

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Background—Factor Xa and factor IIa (thrombin) play roles in thrombotic complications after percutaneous coronary intervention. M118 is a novel low–molecular-weight heparin that has been rationally designed to capture the desired attributes of unfractionated heparin (UFH) and low–molecular-weight heparin: Potent activity against factor Xa and IIa, predictable pharmacokinetics after both intravenous and subcutaneous administration, ability to be monitored by use of point-of-care coagulation assays, and reversibility with protamine sulfate. We performed a phase 2 randomized trial to evaluate the safety and feasibility of M118 in the setting of elective percutaneous coronary intervention.

Methods and Results—Overall, 503 patients undergoing elective percutaneous coronary intervention at 43 centers in the United States and Canada were randomized in an open-label fashion to one of 4 arms: UFH 70 U/kg, M118 50 IU/kg IV, M118 75 IU/kg IV, or M118 100 IU/kg IV. The primary outcome was the composite of death, myocardial infarction, repeat revascularization, stroke, thrombocytopenia, catheter thrombus, bailout use of glycoprotein IIb/IIIa inhibitor, or any bleeding through 30 days. The primary end point occurred in 31.1% of patients randomized to UFH and in 22.7%, 28.3%, and 30.1% of patients randomized to M118 50, 75, and 100 IU/kg, respectively. The primary analysis comparing the rates of the primary end points between the pooled M118 groups versus UFH demonstrated that M118 was noninferior to UFH at preventing percutaneous coronary intervention–related complications (28.4% pooled M118 arms versus 31.1% UFH). The adverse event profiles of M118 and UFH were comparable.

Conclusions—This phase 2 randomized trial demonstrates that M118 is well tolerated and feasible to use as an anticoagulant in patients undergoing elective percutaneous coronary intervention and forms the basis for further investigation of this agent in ischemic heart disease.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00543400. (Circulation. 2010;121:1713-1721.)

Key Words: heparin ■ anticoagulants ■ percutaneous transluminal coronary angioplasty

Percutaneous coronary intervention (PCI) is associated with thrombin generation and its sequelae, such as platelet activation and aggregation and embolization of atherothrombotic debris.1 Anticoagulant therapy can minimize the ischemic sequelae of PCI and the risk of thrombus formation on interventional equipment. Available strategies include the use of unfractionated heparin (UFH), low–molecular-weight heparins (LMWH), factor Xa inhibitors, and direct thrombin inhibitors, all of which have limitations.2 For example, UFH activates platelets,3 does not provide predictable anticoagulation (and requires frequent monitoring), has a narrow therapeutic window,4 is associated with increased bleeding risk compared with other antithrombins,5 and poses a risk for heparin-induced thrombocytopenia. LMWHs, of which enoxaparin is the most studied, provide more predictable levels of anticoagulation than UFH but have little activity against thrombin, are not completely reversible, and cannot be monitored by use of point-of-care assays.6 Fondaparinux, an indirect synthetic factor Xa inhibitor, is associated with reduced bleeding and improved survival in acute coronary syndrome but is not recommended for use during...
PCI because of an increased risk of catheter thrombus. Bivalirudin, a direct thrombin inhibitor, is associated with significant reductions in major bleeding compared with UFH and enoxaparin and is associated with improved survival when used during primary PCI, but it is also associated with increases in periprocedural myocardial infarction (MI) and acute stent thrombosis. Given the clinical priority to reduce ischemia and minimize bleeding risk, a need exists for more efficacious and safer anticoagulants for use during PCI.

Clinical Perspective on p 1721

It has been demonstrated that LMWHs can be engineered to have certain attributes specifically tailored to the intended clinical setting. M118 is a novel LMWH that combines the beneficial properties of UFH and enoxaparin while addressing their respective limitations. It is produced by depolymerization of UFH that is derived from porcine intestinal mucosa. This process significantly reduces molecular weight to a range from 5500 to 9000 Da from the parent UFH molecule and positions the pentasaccharide and thrombin heparin-binding regions on the nonreducing and reducing ends of the molecule, respectively. M118 shows broad anticoagulant activity, including potent activity against factor Xa and thrombin (factor IIa), low polydispersity, subcutaneous bioavailability (∼70% in humans), and predictable subcutaneous and intravenous pharmacokinetics. The anti-Xa to anti-IIa ratio of approximately 1.4:1 remains constant over time in vivo. The plasma half-life of M118 is approximately 1 hour after intravenous bolus injection and 2 to 3 hours after subcutaneous injection. Additionally, M118 does not activate platelets, and its anticoagulant activity can be monitored by standard coagulation assays such as activated clotting time (ACT) and activated partial thromboplastin time; in addition, owing to its charge, it is reversible to subtherapeutic levels with protamine sulfate.

Given these properties, M118 may address many limitations of existing anticoagulants. To demonstrate the safety and feasibility of intravenous M118 in the setting of elective PCI, we performed a phase 2 randomized trial comparing 3 doses of intravenous M118 with a standard dose of intravenous UFH.

Methods

The Evaluation of M118 IN pErCutaneous Coronary inTervention (EMINENCE) trial was a randomized, open-label, multicenter, phase 2 noninferiority trial comparing 3 doses of intravenous M118 (50, 75, and 100 IU/kg) with intravenous UFH (70 U/kg). Forty-three centers from the United States and Canada participated in the study (Appendix A in the online-only Data Supplement).

Patient Population

Patients 19 years of age or older who were undergoing elective PCI were eligible if they had documented stable coronary disease amenable to PCI. Inclusion and exclusion criteria are listed in Table 1.

Randomization

To address potential bias with the open-label design, the block randomization scheme contained a random sequence of the trial treatments. There were several sizes of blocks, and these blocks were in a random order. To protect the integrity of the randomization process, the actual block sizes and their distribution remained confidential. The site coordinator contacted the interactive voice response system by telephone to obtain the treatment assignment.

Table 1. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tr>
<td>Age ≥19 y</td>
<td>ACT &gt;200 seconds before study drug administration</td>
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<tr>
<td>Stable coronary artery disease amenable to PCI</td>
<td>Hemoglobin &lt;10.0 g/dL or hematocrit &lt;30%</td>
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<tr>
<td>Platelet count of &lt;100 000/mm³ or &gt;600 000/mm³</td>
<td>Platelet count of &lt;100 000/mm³ or &gt;600 000/mm³</td>
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<td>Creatinine clearance &lt;30 mL/min</td>
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<tr>
<td>Baseline AST or ALT greater than the upper limit of normal</td>
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<td>MI within 7 days before index PCI</td>
<td>MI within 7 days before index PCI</td>
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<tr>
<td>Known allergies to heparin (including a known history of heparin-induced thrombocytopenia), pork, or pork-containing products</td>
<td>Known allergies to heparin (including receipt of oral anticoagulant therapy)</td>
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<tr>
<td>Hemodynamic instability or untreated severe hypertension at the time of the index PCI</td>
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<tr>
<td>Trauma or major surgery in the 30 days before index PCI, or planned surgery or PCI in the 30 days after index PCI</td>
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<tr>
<td>Receipt of LMWH within the 12 hours before PCI if creatinine clearance is &gt;60 mL/min or within 24 hours before PCI if creatinine clearance is ≤60 mL/min was excluded</td>
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</tr>
<tr>
<td>Planned use of GPI or atherectomy</td>
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</tr>
<tr>
<td>Target vessel is unprotected left main coronary artery, or chronic total occlusion (present for ≥3 months)</td>
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AST indicates aspartate aminotransferase; ALT, alanine aminotransferase.

When a site initially enrolled a patient, the randomization system internally allocated the entire next block to the site without revealing more than 1 assignment at a time. If the site completed the entire block and had another patient to enroll, the site was internally assigned another random block.

Study Protocol

The study comprised 2 phases. In phase A, patients were randomized in a 1:1:1 fashion to intravenous heparin 70 U/kg, intravenous M118 75 IU/kg, or intravenous M118 100 IU/kg. After 5% of the enrollment was completed in the UFH and 75 IU/kg M118 arms, the Data and Safety Monitoring Board reviewed the 24-hour and 14-day end-point data and determined that it was reasonable to add a fourth arm of intravenous M118 50 IU/kg. This began phase B, during which eligible subjects were randomized to UFH or M118 (50, 75, or 100 IU/kg) in unequal proportions to achieve approximately equal numbers of patients in each arm. After the 44th patient was enrolled into the 50 IU/kg M118 arm, the Data and Safety Monitoring Board recommended discontinuation of enrollment into this arm (see below); therefore, the trial reverted back to the phase A 3-arm design.

Study Drugs and Concomitant Medications

Study drug was administered as an intravenous bolus before the coronary guidewire crossed the lesion. For patients assigned to UFH,
the initial dose was 70 U/kg (maximum 5000 U), and a minimum
ACT of 200 seconds was necessary before the lesion could be
crossed. Additional boluses of 20 U/kg could be administered if the
ACT value before or during PCI was <200 seconds. Patients
assigned to any dose of M118 also received the first intravenous
bolus before the guidewire crossed the lesion. Because the optimal
ACT value for M118 during PCI has not been established, additional
M118 boluses were guided by procedure duration and not by specific
ACT values: An additional bolus of one half of the initial M118 dose
was given (25, 37.5, or 50 IU/kg) if the procedure was not completed
30 minutes after the initial bolus. Further boluses at half the initial
dose were given at subsequent 30-minute intervals if needed.

All patients were required to receive 325 mg of aspirin within 12
hours of the index PCI and ≥300 mg of clopidogrel within 6 hours
of the index PCI. Aspirin was then continued at a dose of 75 to 325
mg daily for ≥30 days. Similarly, clopidogrel was continued at a
dose of 75 mg daily for ≥30 days. Continuation of aspirin and
clopidogrel beyond the 30-day period was left to the investigator’s
discretion. Although planned use of glycoprotein Ilb/IIIa inhibitors
(GPIs) was not permitted, they could be used for bailout indications
for clinical or angiographic complications. The choice of GPI was
left to the investigator, and the GPI was administered according to
the package insert of the agent. Arterial closure devices were
permitted at the investigator’s discretion. If a closure device was not
used, vascular access sheaths were removed 4 hours after the last
dose for patients assigned to M118 or when ACT was <160 seconds
for patients assigned to UFH.

ACT Analysis
ACTs were performed with a Hemochron Signature Jr monitor (ITC
Medical, Edison, NJ) at the following time points: (1) After arterial
sheath insertion and before administration of study drug (baseline);
(2) 5 minutes after the bolus; (3) 15 minutes after the bolus; (4) 30
minutes after the bolus; and (5) just before sheath removal, regard-
less of whether an arterial closure device was used. If an arterial
closure device was used, then ACT was also performed 4 hours after
the study drug bolus. In the event a second bolus of study drug was
administered, ACTs were performed per the same schedule listed
above, with the second bolus serving as time zero.

Primary and Secondary End Points
The primary end point was the composite of death, MI, repeat
revascularization, or stroke at 30 days; thrombocytopenia or major or
minor bleeding at 24 hours; intraprocedural catheter thrombus; or
bailout use of GPI. End-point definitions are listed in Appendix B in
the online-only Data Supplement. An independent clinical events
committee adjudicated the MI, stroke, and bleeding end points.

Prospectively defined secondary end points included the primary
end point with the exclusion of minor bleeding, 30-day death or MI,
and 30-day death, MI, or repeat revascularization. The composite
of death, MI, repeat revascularization, or major bleeding was examined
as a post hoc end point, as was the comparison of bleeding
complications defined according to the TIMI (Thrombolysis In
Myocardial Infarction) scale.14

Ethical Considerations
The protocol conformed to the Declaration of Helsinki, all sites
obtained approval from their institutional review or ethics boards,
and all patients gave written informed consent. An independent Data
and Safety Monitoring Board reviewed the data periodically. Ad-
verse events and serious adverse events were classified and reported
in accordance with US Food and Drug Administration regulations.13

Statistical Analysis
The primary comparison was between the UFH arm and the pooled
M118 arms by the intention-to-treat principle. A prior PCI trial that
involved a low-risk population16 showed a rate of death, MI, or
target-vessel revascularization of approximately 4%. Because the
primary end point of EMINENCE included several additional
clinical outcomes, we assumed that the rate of the composite end
point in the control (UFH) arm would be 8%. A sample size of 600
patients (150 patients per arm) provided 93% power to rule out an
absolute increase of 8% in the combined M118 arms with a 1-sided
α=0.05.

Baseline demographic and procedural characteristics were com-
pared by parametric or nonparametric methods as appropriate.
Continuous variables are presented as mean±SD or as medians with
interquartile ranges. Categorical variables are presented as numbers
and percentages. All rates presented assume that if data on a
component of the primary end point were not available, then this
component had not occurred. Sensitivity analyses were also per-
formed on the primary end point by use of 2 assumptions: (1) Missing
components of the composite end points had occurred, and
(2) no assumptions about missing data (intent-to-treat). A series of
secondary comparisons were also performed that consisted of nonin-
feriority analyses of each M118 dose with UFH, as well as
comparisons of 30-day death or MI and death, MI, or repeat
revascularization. Rates of the primary and secondary end points are
reported by the Kaplan-Meier method.

The Data and Safety Monitoring Board convened after the 44th
patient enrolled in the M118 50-IU/kg arm died of multisystem organ
failure within 24 hours of the index PCI. After reviewing clinical
and angiographic data, the Data and Safety Monitoring Board could not
definitively attribute the death to complications from PCI; however,
they could not exclude the possibility that the lowest dose of M118
may have been causally related to the event and believed that it could
limit the practicality of future enrollment into the trial at the 50-IU/kg
dose of M118. Therefore, they recommended that random-
ization into this arm be discontinued, and the sponsor and Steering
Committee concurred. Additional prospectively defined secondary
comparisons were made between the UFH arm and the pooled M118
arms that excluded the 50-IU/kg dose.

Results
Patient Population
Figure 1 displays the flow of patients through the trial. Owing
to early discontinuation of enrollment into the M118 50-
IU/kg arm, a total of 503 patients were randomized, of whom
497 underwent cardiac catheterization, 492 underwent PCI,
and 488 received the study drug. Table 2 lists the baseline
clinical and procedural characteristics of the trial population.
There were no substantive differences across treatment
groups. The median age of the subjects enrolled was 63.8
years, and 27.6% were females. Six percent of the patients
had a history of prior stroke, 34.4% had a history of MI,
59.4% had prior revascularization (PCI or coronary artery
bypass graft), 9.5% had a history of congestive heart failure,
and 33.0% had a history of diabetes mellitus. Table 2 also
lists the extent of coronary artery disease in the trial popula-
tion: 63.8% had 1-vessel disease, whereas 12.1% had 3-vessel
disease. The predominant vascular access approach was trans-
memoral (99.6%) with 6F sheaths. Most patients (65.5%) had
only 1 lesion treated.

ACTs demonstrated a dose-dependent increase in the
M118 arms at all time points (Figure 2). The median ACT
value 5 minutes after the initial study drug bolus was 300.5,
210.0, 246.0, and 279.5 seconds in the UFH arm and the 50-
75-, and 100-IU/kg M118 arms, respectively. Among patients
who did not receive a closure device, the median ACT values
before sheath removal were 155.0, 158.0, 160.0, and 169.0
seconds in the UFH arm and the 50-, 75-, and 100-IU/kg
M118 arms, respectively.
Study Drug and Concomitant Medications

Table 3 lists the angiographic outcomes and treatments received during the index PCI and the concomitant antiplatelet therapy prescribed before and after the procedure. The appropriate randomized treatment was administered to 98.0% to 100% of enrolled patients. The predominant aspirin dose used before PCI was 325 mg, and most patients received 300 mg of clopidogrel before PCI. Drug-eluting stents were used more often than bare-metal stents, and 53.5% of patients received an arterial closure device.

Outcomes

Table 4 lists the incidence of the primary and secondary end points across treatment groups. The rate of the primary end point was comparable between the UFH arm and the combined M118 arms. There was 1 catheter thrombus in the UFH arm and no episodes of catheter thrombus in any of the M118 groups. The bailout use of GPI was more common in the UFH arm than in either the combined M118 arms or each individual arm of M118. Table 5 lists the primary and secondary analyses of noninferiority and shows that both the combined...
M118 group and each dose of M118 met the test of noninferiority with UFH. Figure 3 shows the Kaplan-Meier rates of the primary end point for the UFH and combined M118 arms (with and without the 50-IU/kg arm). Figure 4 displays the Kaplan-Meier rates of the prospectively defined secondary end point of death, MI, or repeat revascularization for the UFH and combined M118 arms, with and without the 50-IU/kg arm. Sensitivity analyses that used the 2 other assumptions for missing data were consistent with the overall results (data not shown).

With respect to bleeding complications, the incidence of protocol-defined REPLACE-2 (Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events) major and minor bleeding was slightly higher in the combined M118 group than in the UFH group, and there was a stepwise increase in major plus minor bleeding as the dose of M118

Table 3. Angiographic Outcomes and Treatments

<table>
<thead>
<tr>
<th></th>
<th>UFH (n=151)</th>
<th>50 IU/kg M118 (n=44)</th>
<th>75 IU/kg M118 (n=152)</th>
<th>100 IU/kg M118 (n=156)</th>
<th>Combined M118 (n=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure success</strong></td>
<td>133/143 (93.0)</td>
<td>41/42 (97.6)</td>
<td>140/144 (97.2)</td>
<td>144/152 (94.7)</td>
<td>325/338 (96.2)</td>
</tr>
<tr>
<td><strong>Ablatory closure</strong></td>
<td>1/149 (0.7)</td>
<td>1/44 (2.3)</td>
<td>0/150 (0.0)</td>
<td>0/154 (0.0)</td>
<td>1/348 (0.3)</td>
</tr>
<tr>
<td><strong>No reflow</strong></td>
<td>0/149 (0.0)</td>
<td>0/44 (0.0)</td>
<td>0/150 (0.0)</td>
<td>0/154 (0.0)</td>
<td>0/348 (0.0)</td>
</tr>
<tr>
<td><strong>New thrombus</strong></td>
<td>0/149 (0.0)</td>
<td>1/44 (2.3)</td>
<td>0/150 (0.0)</td>
<td>0/154 (0.0)</td>
<td>1/348 (0.3)</td>
</tr>
<tr>
<td><strong>Dissection</strong></td>
<td>4/149 (2.7)</td>
<td>0/44 (0.0)</td>
<td>1/150 (0.7)</td>
<td>2/154 (1.3)</td>
<td>3/348 (0.9)</td>
</tr>
<tr>
<td><strong>Prolonged ischemia</strong></td>
<td>1/149 (0.7)</td>
<td>0/44 (0.0)</td>
<td>0/150 (0.0)</td>
<td>0/154 (0.0)</td>
<td>0/348 (0.0)</td>
</tr>
<tr>
<td><strong>Side-branch closure</strong></td>
<td>2/149 (1.3)</td>
<td>0/44 (0.0)</td>
<td>0/150 (0.0)</td>
<td>0/154 (0.0)</td>
<td>0/348 (0.0)</td>
</tr>
<tr>
<td><strong>Requirement for CABG</strong></td>
<td>2/149 (1.3)</td>
<td>0/44 (0.0)</td>
<td>0/150 (0.0)</td>
<td>0/154 (0.0)</td>
<td>0/348 (0.0)</td>
</tr>
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</table>

**Treatments**

| Drug-eluting stent used | 110/132 (83.3) | 33/41 (80.5) | 111/132 (84.1) | 114/136 (83.8) | 258/309 (83.5) |
| Arterial closure device used | 79/149 (53.0) | 19/44 (43.2) | 83/150 (55.3) | 85/154 (55.2) | 187/348 (53.7) |
| Received correct randomized anticoagulant, % | 98.6 | 100.0 | 98.0 | 98.7 | 98.6 |
| Received >1 dose of study drug (UFH or M118)* | 16/146 (11.0) | 15/43 (34.9) | 40/148 (27.0) | 42/151 (27.8) | 97/342 (28.4) |
| Mean dose of study drug received, U/kg body weight | 72.3 | 61.0 | 88.0 | 116.6 | N/A |

**ASA dose 325 mg** | 134/149 (89.9) | 32/43 (74.4) | 138/152 (90.8) | 136/154 (88.3) | 306/349 (87.7) |
| **ASA dose <325 mg** | 15/149 (10.1) | 11/43 (25.6) | 13/152 (8.6) | 18/154 (11.7) | 42/349 (12.0) |
| **Clopidogrel load <300 mg** | 10/148 (6.8) | 3/43 (7.0) | 13/151 (8.6) | 8/152 (5.3) | 24/346 (6.9) |
| **Clopidogrel load ≥300 mg** | 138/148 (93.2) | 40/43 (93.0) | 138/151 (91.4) | 144/152 (94.7) | 322/346 (93.1) |

*Additional boluses of M118 at half of the randomized dose were to be given every 30 minutes by protocol; additional boluses of UFH could be given if the ACT was <200 seconds.

ASA indicates acetylsalicylic acid; CABG, coronary artery bypass graft; N/A, not applicable; and UFH, unfractionated heparin.
increased (Table 4). The post hoc analysis of TIMI major and minor bleeding showed no significant differences between UFH and the combined M118 group. The incidence of protocol-defined major bleeding did not differ between the UFH and combined M118 groups when either the REPLACE-2 or TIMI definition of major bleeding was used; the increase in bleeding in the combined M118 group was driven by higher protocol-defined minor bleeding. The vast majority of bleeding complications were related to the vascular access site. The rate of blood transfusion was very low overall (2.6% among patients randomized to UFH and 0.6% among patients randomized to M118).

The incidence of serious adverse events in the UFH and combined M118 groups was 13.2% and 9.9%, respectively. The rates of any adverse events in the UFH and combined M118 arms were 76.8% and 75.6%, respectively.

### End Points After Exclusion of the 50-IU/kg M118 Arm

A series of secondary analyses were performed to examine the rates of the primary and secondary end points after exclusion of the 44 patients assigned to the 50-IU/kg dose (Table 6). The results were consistent with those of the primary analysis that included the 50-IU/kg dose.

### Discussion

The results of the phase 2 EMINENCE trial demonstrate that M118 is well tolerated and feasible to use as anticoagulant therapy during PCI. It exhibits a dose-dependent increase in...
ACT and is noninferior to UFH with respect to a broad composite of end points that reflect PCI-related complications. In addition to clinical outcomes, angiographic outcomes were excellent and comparable between UFH and M118.

M118 is a novel LMWH that has been rationally designed to have properties suitable for treatment of acute ischemic heart disease. Its activity against thrombin (factor IIa) is likely important to reduce thrombotic complications during PCI in the setting of acute coronary syndrome, in which a thrombin-rich clot is present in 1 or more coronary arteries, and during PCI, in which thrombin is generated as a consequence of balloon trauma to the endothelium. Thrombin plays an important role in the conversion of fibrinogen into fibrin, the activation of platelets, and the subsequent amplification of the coagulation cascade via the intrinsic pathway. An added benefit of this anti-IIa activity is a highly correlated response to ACT, which allows for point-of-care monitoring of anticoagulant levels generated by M118. This is a distinct advantage over other LMWH preparations. Other properties, including reduced polydispersity, lower molecular weight, and charge, contribute to its predictable pharmacokinetics, subcutaneous bioavailability, and reversibility by protamine sulfate, respectively.

Several aspects of the EMINENCE trial deserve comment. First, M118 exhibited a dose-dependent increase in the ACT: The value 5 minutes after the initial bolus was across all doses. All of the values, however, were lower than those seen with UFH, which was an expected finding. Given that anti-Xa activity is not reflected in the ACT and that the anti-Xa to anti-IIa ratio of M118 is 1.4:1 (compared with 1:1 for UFH), M118 would be expected to have greater anticoagulant activity with doses that result in lower ACT values than UFH. Second, the rates of protocol-defined (ie, REPLACE-2) major bleeding were similar across groups; the rates of protocol-defined minor bleeding were higher in the M118 arms. Indeed, the dose-dependent increase in the rate of the primary end point

Figure 3. Time-to-event curves for the primary end point in the UFH arm and the combined M118 arms with and without the 50-IU/kg dose of M118.

Figure 4. Time-to-event curves for the prospectively defined secondary end point of death, MI, and repeat revascularization in the UFH and combined M118 arms with and without the 50-IU/kg dose of M118.
Bleeding complications, such as enoxaparin and bivalirudin will need to be explored in adequately powered phase 3 trials. With increasing doses of M118 was driven by higher rates of minor bleeding. Given the unblinded nature of the trial, the explanation of these differences is likely complex, but because most bleeding events were related to the vascular access site, it is possible that the comparatively higher ACT values at the time of sheath removal accounted for the minor bleeding. This observation suggests that to reduce minor bleeding complications, femoral sheath removal after M118 may need to occur at lower ACT values than with UFH. Indeed, the ACT values in all of the M118 arms decreased over time but were still higher than that seen with UFH at the time of sheath removal. This issue, and the effect of additional antiplatelet therapies such as prasugrel or GPI on bleeding complications, will need to be explored in an adequately powered phase 3 trial. Bleeding defined according to the TIMI scale did not differ across the study arms. Third, the rates of the primary end point were higher than expected and higher than in previous elective PCI trials. This is likely due to the inclusion of other clinical events such as thrombocytopenia and REPLACE-2 major and minor bleeding in the primary end point of the EMINENCE trial that were not included in the primary end points of prior larger trials, as well as to differences in the definitions of the end points themselves. Fourth, the incidence of MI was higher with the 50-IU/kg dose (9.3%) than with UFH (6.2%), whereas the overall incidence of bleeding was lower (13.6% versus 17.2%); however, given the relatively small number of patients studied in this arm, it is difficult to draw firm conclusions about the 50-IU/kg dose of M118. Taken together, these data suggest that the range of 50- to 100-IU/kg doses was appropriate to study. Further refinement of the dose range in future trials should allow identification of the optimal dose to maximize benefit and minimize risk. Although the study was neither designed nor powered to draw conclusions about comparative efficacy, there was a pattern of lower rates of death, MI, or repeat revascularization, as well as death, MI, repeat revascularization, or major bleeding (the so-called net clinical benefit), as the dose of M118 increased. These differences in the secondary end points were not tested formally; however, they suggest that a dose range for M118 of 75 to 100 IU/kg is reasonable to study in a larger phase 3 trial. There are some important limitations of the EMINENCE trial. Given that this was a phase 2 trial, the present study had limited statistical power to definitively compare individual doses of M118 with UFH. A noninferiority margin similar to that used in EMINENCE has been used previously in phase 2 trials of new anticoagulants in PCI. Importantly, because the event rate in the control UFH arm was much higher than anticipated (31.1% versus the assumed 8%), the prespecified noninferiority margin of an absolute 8% difference reflects substantially less than a doubling of the control group. The noninferiority margin used in the present study, therefore, actually excludes a narrower relative difference than originally assumed. In addition, the open-label design of EMINENCE may have influenced the investigator classification of events. To address this limitation, we employed an independent clinical events committee who adjudicated all suspected MIs, strokes, and bleeding events. Adjunctive therapies such as routine use of GPI were not allowed by protocol; however, previous trials have not demonstrated a benefit of GPI in elective PCI when oral dual-antiplatelet therapy is given in advance of the procedure. Finally, EMINENCE was a phase 2 trial and by design included low-risk patients. The safety and efficacy of M118 for the treatment of higher-risk patients and in combination with GPI and other emerging antiplatelet agents will need to be evaluated in adequately powered phase 3 trials. Similarly, direct comparisons of M118 to other anticoagulants such as enoxaparin and bivalirudin will need to be explored in the future.

### Conclusions

In this phase 2 study of elective PCI, a range of doses of intravenous M118 were comparable to UFH at preventing a

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**Table 6. Rates of Primary and Secondary End Points in UFH and Combined M118 Arms With Exclusion of 50-IU/kg M118 Dose**

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>Combined M118 Excluding 50-IU/kg M118 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UFH (n=151)</td>
</tr>
<tr>
<td>30-Day death</td>
<td>0/148 (0.0)</td>
</tr>
<tr>
<td>30-Day MI</td>
<td>9/145 (6.2)</td>
</tr>
<tr>
<td>30-Day repeat revascularization</td>
<td>4/145 (2.8)</td>
</tr>
<tr>
<td>30-Day stroke</td>
<td>0/145 (0.0)</td>
</tr>
<tr>
<td>24-Hour thrombocytopenia</td>
<td>4/151 (2.6)</td>
</tr>
<tr>
<td>24-Hour major plus minor bleeding</td>
<td>26/151 (17.2)</td>
</tr>
<tr>
<td>Bailout use of GPI during procedure</td>
<td>12/149 (8.1)</td>
</tr>
<tr>
<td>Catheter thrombus during procedure</td>
<td>1/146 (0.7)</td>
</tr>
</tbody>
</table>

Secondary end points

<table>
<thead>
<tr>
<th>Primary end point excluding minor bleeding</th>
<th>Combined M118 Excluding 50-IU/kg M118 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UFH (n=151)</td>
</tr>
<tr>
<td>Death or MI</td>
<td>9/151 (6.0)</td>
</tr>
<tr>
<td>Death, MI, or repeat revascularization</td>
<td>13/151 (8.6)</td>
</tr>
<tr>
<td>Death, MI, repeat revascularization, or major bleeding*</td>
<td>13/151 (8.6)</td>
</tr>
</tbody>
</table>

Bleeding complications

<table>
<thead>
<tr>
<th>Protocol-defined major bleeding</th>
<th>Combined M118 Excluding 50-IU/kg M118 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol-defined minor bleeding</td>
<td>2/151 (1.3)</td>
</tr>
<tr>
<td>TIMI major bleeding*</td>
<td>24/151 (15.9)</td>
</tr>
<tr>
<td>TIMI minor bleeding*</td>
<td>1/144 (0.7)</td>
</tr>
<tr>
<td>TIMI minimal bleeding*</td>
<td>2/144 (1.4)</td>
</tr>
<tr>
<td>Red cell transfusion</td>
<td>4/151 (2.6)</td>
</tr>
</tbody>
</table>

Values are n/N (%). *Examined post hoc.
broad composite of PCI-related complications. A dose range of 75 to 100 IU/kg appears promising and should be tested further in a phase 3 trial.

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Disclosures
Dr Rao has served on the speakers' bureau of and received consulting honoraria from sanofi-aventis, Bristol-Myers Squibb, and The Medicines Company and has received research funding from Momenta Pharmaceuticals Inc, Portola Pharmaceuticals Inc, and Cordis Corp. Dr Melloni has received research funding from Momenta Pharmaceuticals. Dr Tanguay has received research support and consulting honoraria from Momenta Pharmaceuticals Inc, Portola Pharmaceuticals Inc, and Cordis Corp. Dr Rao has served on the speakers' bureau of and received consulting honoraria and stock options from Momenta Pharmaceuticals. Dr Alexander has received research funding from Momenta Pharmaceuticals Inc, Portola Pharmaceuticals Inc, and Cordis Corp. Dr Schomig has received research funding from Momenta Pharmaceuticals. Dr StuckImmediate has received consulting honoraria from Momenta Pharmaceuticals. Dr Becker has received research funding from and has served as a consultant for Momenta Pharmaceuticals. Drs Fier and Roach are employed by Momenta Pharmaceuticals. Dr Becker has received research funding from and has served on a scientific advisory board for Momenta Pharmaceuticals. The remaining authors report no conflicts.

References

CLINICAL PERSPECTIVE
M118 is a novel low–molecular-weight heparin that has been rationally designed to capture the desired attributes of both unfractionated heparin and low–molecular-weight heparin: Potent activity against both factor Xa and IIa, predictable pharmacokinetics after both intravenous and subcutaneous administration, ability to be monitored by use of point-of-care coagulation assays, and reversibility with protamine sulfate. We performed a phase 2 randomized trial to evaluate the safety and feasibility of M118 in the setting of elective percutaneous coronary intervention. The results of the EMINENCE trial demonstrate that M118 is well tolerated and feasible to use as anticoagulant therapy during percutaneous coronary intervention. It exhibits a dose-dependent increase in the activated clotting time and is noninferior to unfractionated heparin with respect to a broad composite of end points that reflect complications related to percutaneous coronary intervention. In addition to clinical outcomes, angiographic outcomes were excellent and comparable between unfractionated heparin and M118. Although a range of doses of intravenous M118 were comparable to unfractionated heparin at preventing a broad composite of percutaneous coronary intervention–related complications, we conclude that a dose range of 75 to 100 IU/kg appears most promising and should be tested further in a phase 3 trial.
Evaluation of a New Heparin Agent in Percutaneous Coronary Intervention: Results of the Phase 2 Evaluation of M118 IN pErcutaNeous Coronary intErvention (EMINENCE) Trial

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SUPPLEMENTAL MATERIAL

Appendix A – Committees and Sites for the EMINENCE Trial

**Steering Committee:** Sunil V. Rao, MD, Chiara Melloni, MD, MHS, Richard C. Becker, MD, Neal S. Kleiman, MD, Vladimir Dzavik, MD, Jean Francois Tanguay, MD, Marc S. Cohen, MD, Carey Kimmelstiel, MD, Ian Fier, MBA, James Roach, MD.

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Appendix B – Endpoint Definitions

1. Myocardial infarction

Events occurring within 2 days of the index procedure:
   a) new pathological electrocardiographic Q-waves in ≥2 contiguous leads OR
   b) a creatine kinase muscle-brain (CKMB) fraction ≥3 times the upper limit of normal

Events occurring >2 days after the PCI:
   a) new pathological electrocardiographic Q-waves in ≥2 contiguous leads, OR
   b) a CKMB value above the upper limit of normal, OR
   c) a troponin I or T value above the upper limit of normal

Events after surgical coronary vessel revascularization:
   a) new pathological electrocardiographic Q-waves in ≥2 contiguous leads OR
   b) a CKMB fraction ≥5 times the upper limit of normal.

2. Stroke—a new, sudden, focal neurological deficit resulting from a presumed cerebrovascular cause that was unresolved within 24 hours and not due to a readily identifiable cause such as tumor or seizure. Stroke could also be diagnosed by the presence of a new ischemic lesion found on brain imaging that was consistent with the symptoms regardless of symptom duration.

3. Catheter thrombus—any evidence of thrombus on the guide catheter, coronary guidewire, or coronary device that was felt not to be associated with a coronary lesion or dissection.
4. Major bleeding (defined according to the REPLACE-2 scale) — Transfusion of >2 units of packed red cells or whole blood, intracranial hemorrhage, retroperitoneal hemorrhage, decrease in hemoglobin >4 g/dl (or an absolute decrease in hematocrit >12%) with no identified bleeding site, or spontaneous or non-spontaneous blood loss associated with a decrease in hemoglobin >3 g/dl (or absolute decrease in hematocrit > 10%).

5. Minor bleeding — any observed bleeding that did not meet criteria for major bleeding.

6. Thrombocytopenia — platelet count <100,000/mm³ or a ≥50% decrease from the pre-procedure value occurring within 24 hours of the index procedure.

7. Repeat revascularization — any revascularization procedure occurring within 30 days of the index procedure.
   a. Target vessel revascularization was defined as either PCI or CABG involving any vessel that was treated during the index PCI; urgent revascularization was defined as either PCI or CABG that was the result of ischemic symptoms occurring after the completion of the index PCI.