

# Influence of Renal Function on the Efficacy and Safety of Fondaparinux Relative to Enoxaparin in Non–ST-Segment Elevation Acute Coronary Syndromes

Keith A.A. Fox, MBChB; Jean-Pierre Bassand, MD; Shamir R. Mehta, MD; Lars Wallentin, MD, PhD; Pierre Theroux, MD; Leopoldo Soares Piegas, MD, PhD; Vicent Valentin, MD; Tiziano Moccetti, MD; Susan Chrolavicius, BA; Rizwan Afzal, MSc; and Salim Yusuf, MD, DPhil, on behalf of the OASIS 5 Investigators

**Background:** A recent randomized, controlled trial, the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS 5) trial, reported that major bleeding was 2-fold less frequent with fondaparinux than with enoxaparin in acute coronary syndromes (ACS). Renal dysfunction increases the risk for major bleeding.

**Objective:** To compare the efficacy and safety of fondaparinux and enoxaparin over the spectrum of renal dysfunction observed in the OASIS 5 trial.

**Design:** Subgroup analysis of a randomized, controlled trial.

**Setting:** Patients presenting to the hospital with non–ST-segment elevation ACS.

**Patients:** 19 979 of the 20 078 patients in the OASIS 5 trial in whom creatinine was measured at baseline.

**Measurements:** Death, myocardial infarction, refractory ischemia, and major bleeding were evaluated separately and as a composite end point at 9, 30, and 180 days. Glomerular filtration rate (GFR) was calculated by using the Modification of Diet in Renal Disease formula.

**Results:** The absolute differences in favor of fondaparinux (efficacy and safety) were most marked in patients with a GFR less than 58

mL/min per 1.73 m<sup>2</sup>; the largest differences occurred in major bleeding events. At 9 days, death, myocardial infarction, or refractory ischemia occurred in 6.7% of patients receiving fondaparinux and 7.4% of those receiving enoxaparin (hazard ratio, 0.90 [95% CI, 0.73 to 1.11]); major bleeding occurred in 2.8% and 6.4%, respectively (hazard ratio, 0.42 [CI, 0.32 to 0.56]). Statistically significant differences in major bleeding persisted at 30 and 180 days. The rates of the composite end point were lower with fondaparinux than with enoxaparin in all quartiles of GFR, but the differences were statistically significant only among patients with a GFR less than 58 mL/min per 1.73 m<sup>2</sup>.

**Limitations:** Subgroup analyses warrant caution; the study was powered to detect noninferiority at 9 days. Fondaparinux is not approved for use in patients with ACS in the United States.

**Conclusions:** The benefits of fondaparinux over enoxaparin when administered for non–ST-segment elevation ACS are most marked among patients with renal dysfunction and are largely explained by lower rates of major bleeding with fondaparinux.

*Ann Intern Med.* 2007;147:304-310.

For author affiliations, see end of text.

www.annals.org

The development of more effective antithrombotic therapies for acute coronary syndromes (ACS) has focused primarily on reducing ischemic and thrombotic complications. However, the balance between efficacy and safety is critical in determining optimal antithrombotic treatment for non–ST-segment elevation ACS. Such patients exhibit a spectrum of renal dysfunction severity (1–3). Renal dysfunction not only amplifies risks for death, stroke, and other cardiac complications but also increases the risk for bleeding (3–5). The presence and degree of renal dysfunction may therefore influence the balance between safety and efficacy of antithrombotic agents. Evidence-based

guidelines support the use of antiplatelet and antithrombotic therapies, but currently available agents also increase the risk for bleeding.

Studies in patients with renal dysfunction have demonstrated increased cardiovascular risk (6–10). In registry studies, renal insufficiency is a powerful predictor of risk among patients admitted for acute myocardial infarction (MI) (3–5) or non–ST-segment elevation ACS (11). As creatinine clearance declines, the rate of major bleeding events increases, even among patients not dependent on dialysis (5).

The most widely used antithrombotics in non–ST-segment elevation ACS are unfractionated heparin and low-molecular-weight heparin. A meta-analysis suggests that in the context of thrombolysis for ST-segment elevation MI, enoxaparin may be modestly superior to unfractionated heparin in reducing death or MI and cause similar rates of bleeding (12). In the context of interventional therapy, similar efficacy but a higher rate of bleeding was observed in the Superior Yield of the New Strategy of Enoxaparin Revascularization and Glycoprotein IIb/IIIa trial (13). At lower doses, enoxaparin had efficacy similar to that of heparin without an increase in bleeding in the

See also:

## Print

Editors' Notes . . . . . 305

## Web-Only

Appendix Table

Appendix Figure

Conversion of graphics into slides

Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention trial (14). The use of glycoprotein IIb/IIIa antagonists may also increase the risk for bleeding (4, 13, 14).

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS 5) trial compared fondaparinux (a selective factor Xa inhibitor) with enoxaparin for short- and long-term efficacy and safety in 20 078 patients with non-ST-segment elevation ACS (15). The trial met the predefined noninferiority criteria. It established that fondaparinux was noninferior to enoxaparin for the primary end point of death, MI, or refractory ischemia at 9 days (15). With fondaparinux, major bleeding was substantially reduced, and there were statistically significantly fewer deaths and strokes during long-term follow-up (15).

The OASIS 5 investigation provides the opportunity to test the safety (major bleeding) and efficacy (death, MI, and refractory ischemia) of fondaparinux versus enoxaparin in a large sample of patients with a spectrum of renal function. Enoxaparin is primarily metabolized by the liver through desulfation or depolymerization into lower-molecular-weight species, but renal clearance of active and non-active fragments represents about 40% of the administered dose. The data sheet recommends adjustment in patients with severe renal impairment (creatinine clearance <0.5 mL/s [ $<30$  mL/min]). Fondaparinux is excreted by the kidney without previous metabolism.

We hypothesize that bleeding risk is influenced by the degree of renal dysfunction and that the excess bleeding risk and mortality observed with enoxaparin are related to the severity of renal dysfunction.

## METHODS

Details of the design and methods of the OASIS 5 study are reported elsewhere (16). In brief, OASIS 5 was a randomized, double-blind, placebo-controlled, parallel-group trial of fondaparinux versus enoxaparin in patients with unstable angina or non-ST-segment elevation MI (**Appendix Figure**, available at [www.annals.org](http://www.annals.org)). Patients were eligible if they presented to the hospital with symptoms of ACS without persistent ST-segment elevation but with at least 2 of the following criteria: age 60 years or older, troponin T or I or creatine kinase-MB levels above the upper limit of normal, or electrocardiographic changes indicating ischemia (ST-segment depression  $>1$  mm in 2 contiguous leads, T-wave inversion  $>3$  mm, or a dynamic shift in ST-segment or transient ST-segment elevation) (16). Patients were excluded if they had a contraindication to low-molecular-weight heparin, including a history of hemorrhagic stroke within the previous 12 months or severe renal insufficiency (serum creatinine level  $>3$  mg/dL [ $>265$   $\mu$ mol/L]).

The study was powered to demonstrate noninferiority of fondaparinux compared with enoxaparin at 9 days (16). The noninferiority margin excluded a loss of benefit of 18.5% (half of the lower boundary of the 95% CI for any

### Context

These researchers hypothesized that the benefit of fondaparinux versus enoxaparin for patients with non-ST-segment acute coronary syndromes would be greatest among patients whose risk for bleeding was greater because of renal dysfunction.

### Contribution

Among patients with a glomerular filtration rate (GFR) less than 58 mL/min per 1.73 m<sup>2</sup>, fondaparinux had lower rates of combined death, major bleeding, myocardial infarction, or refractory angina compared with enoxaparin: 8.8% vs. 12.5% (hazard ratio, 0.69 [95% CI, 0.58 to 0.82]) at 9 days, 12.9% vs 17.6% (hazard ratio, 0.71 [95% CI, 0.62 to 0.82]) at 30 days, and 21.3% vs 24.7% (hazard ratio, 0.83 [CI, 0.74 to 0.93]) at 180 days. The differences were not statistically significant among patients with a GFR greater than 58 mL/min per 1.73 m<sup>2</sup>.

### Implication

In non-ST-segment elevation acute coronary syndromes, the net benefits of fondaparinux compared with enoxaparin are most marked among patients with a GFR less than 58 mL/min per 1.73 m<sup>2</sup>.

—The Editors

heparin vs. control) (12). Patients were followed for a minimum of 90 days and a maximum of 180 days, and pre-specified secondary outcomes included death, MI, and refractory ischemia (individually and their composite). Prespecified safety outcomes included major bleeding events (defined as clinically overt bleeding that is fatal, symptomatic and intracranial, retroperitoneal, or intraocular; results in a decrease in hemoglobin level of  $>30$  g/L; or that requires transfusion of  $>2$  units of red blood cells) (16). The balance of efficacy and safety was analyzed by combining primary safety and efficacy outcomes. All events were adjudicated by a committee blinded to treatment allocation.

The study drugs (fondaparinux, 2.5 mg once daily, or enoxaparin, 1 mg/kg of body weight twice daily) were administered during hospitalization for a minimum of 2 days and for up to 8 days or hospital discharge. Fondaparinux is not currently approved by the U.S. Food and Drug Administration for use in patients with ACS. For patients with creatinine clearance less than 0.5 mL/s ( $<30$  mL/min), the enoxaparin dosage was reduced to 1 mg/kg once daily. The median duration of therapy was 5.2 days.

This subsidiary analysis was undertaken to examine the effect of renal dysfunction. The study sample was stratified according to quartiles of GFR, consistent with the Second National Health and Nutrition Examination Survey on Mortality (6), as estimated by using the Modification of Diet in Renal Disease formula (17, 18).

**Statistical Analysis**

Of the 20 078 patients randomly assigned in the OASIS 5 trial, the current analysis includes 19 979 patients in whom creatinine was measured at baseline. The event rates presented were calculated by using the Kaplan–Meier method. The treatment effect was assessed in each quartile of creatinine clearance by using a Cox proportional hazards model. Tests for interaction were applied to examine whether the treatment differed by GFR. The effect of creatinine clearance was explored by comparing event rates in the highest quartile of GFR with that of the lowest.

**Role of the Funding Source**

The study was conducted independently by the Steering Committee and the Population Health Research Institute, McMaster University, and Hamilton Health Sciences, Hamilton, Ontario, Canada. The conduct of the trial, analysis of the data, and writing of the manuscript were done independently of the study sponsor.

**RESULTS**

**Patient Characteristics**

Table 1 shows the baseline characteristics of study patients by quartile of GFR. The distribution of GFR was well balanced by treatment group: In the enoxaparin and fondaparinux groups, respectively, 12.9% and 12.8% had a GFR less than 58 mL/min per 1.73 m<sup>2</sup>, 12.0% and 12.3% had a GFR from 58 to less than 71 mL/min per 1.73 m<sup>2</sup>, 12.6% and 12.5% had a GFR from 71 to less than 86 mL/min per 1.73 m<sup>2</sup>, and 12.5% and 12.5% had a GFR greater than 86 mL/min per 1.73 m<sup>2</sup>.

**Renal Dysfunction and Outcome**

At 9 days, the combined efficacy outcome of death, MI, or refractory ischemia did not differ statistically significantly between the enoxaparin and fondaparinux groups (criteria for noninferiority were satisfied). There was also no statistically significant difference in efficacy among individual quartiles of GFR (Table 2 and Appendix Table, available at [www.annals.org](http://www.annals.org)). Tests for interaction were not statistically significant.

**Table 1. Key Baseline Characteristics and Management\***

Characteristic	Glomerular Filtration Rate			
	<58 mL/min per 1.73 m <sup>2</sup> (n = 5141)	58 to <71 mL/min per 1.73 m <sup>2</sup> (n = 4845)	71 to <86 mL/min per 1.73 m <sup>2</sup> (n = 5012)	≥86 mL/min per 1.73 m <sup>2</sup> (n = 4996)
Mean age (SD), y	72.4 (8.9)	68.1 (9.5)	64.7 (10.4)	61.0 (11.3)
Men, n (%)	2309 (44.9)	2819 (58.2)	3465 (69.1)	3737 (74.8)
Heart rate (SD), beats/min	74.4 (13.9)	72.9 (13.5)	72.1 (13.2)	72.6 (13.3)
Mean systolic blood pressure (SD), mm Hg	137.9 (23.2)	137.1 (22.5)	136.1 (22.2)	134.7 (21.6)
Medical history, n (%)				
Myocardial infarction	1652 (32.1)	1275 (26.3)	1202 (24.0)	1021 (20.4)
CABG or PCI	993 (19.3)	873 (18.0)	823 (16.4)	718 (14.4)
Stroke	441 (8.6)	320 (6.6)	265 (5.3)	211 (4.2)
Heart failure	1180 (23.0)	671 (13.8)	463 (9.2)	461 (9.2)
Hypertension	4136 (80.5)	3387 (69.9)	3072 (61.3)	2855 (57.1)
Diabetes	1769 (34.4)	1201 (24.8)	1039 (20.7)	1049 (21.0)
ECG compatible with ischemia	4115 (80.0)	3869 (79.9)	4028 (80.4)	4026 (80.6)
ST-segment depression ≥1 mm	2871 (55.8)	2502 (51.6)	2457 (49.0)	2374 (47.5)
Medications at random assignment, n (%)				
Aspirin	4117 (80.1)	3794 (78.3)	3871 (77.2)	3818 (76.4)
Clopidogrel or ticlopidine	1573 (30.6)	1475 (30.4)	1596 (31.8)	1634 (32.7)
Unfractionated heparin	934 (18.2)	812 (16.8)	859 (17.1)	947 (19.0)
Low-molecular-weight heparin	1553 (30.2)	1489 (30.7)	1630 (32.5)	1637 (32.8)
ACE inhibitor or ARB	3202 (62.3)	2579 (53.2)	2283 (45.6)	2168 (43.4)
β-Blocker	3200 (62.2)	2884 (59.5)	2947 (58.8)	2916 (58.4)
Lipid-lowering agent	2093 (40.7)	1921 (39.6)	1888 (37.7)	1780 (35.6)
Medications in hospital after random assignment, n (%)				
Aspirin	4974 (96.8)	4712 (97.3)	4904 (97.8)	4910 (98.3)
Clopidogrel or ticlopidine	3240 (63.0)	3237 (66.8)	3436 (68.6)	3571 (71.5)
Unfractionated heparin	798 (15.5)	737 (15.2)	814 (16.2)	832 (16.7)
Low-molecular-weight heparin	887 (17.3)	834 (17.2)	871 (17.4)	825 (16.5)
β-Blocker	4372 (85.0)	4252 (87.8)	4422 (88.2)	4439 (88.9)
Lipid-lowering agent	3825 (74.4)	3836 (79.2)	4067 (81.1)	4063 (81.3)
Procedures in hospital, n (%)				
Coronary angiography	2743 (53.4)	3053 (63.0)	3368 (67.2)	3508 (70.2)
PCI	1371 (26.7)	1612 (33.3)	1863 (37.2)	2021 (40.5)
CABG	429 (8.3)	451 (9.3)	489 (9.8)	487 (9.7)

\* ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass grafting; ECG = electrocardiogram; PCI = percutaneous coronary intervention.

Table 2. Outcomes at 9, 30, and 180 Days, by Glomerular Filtration Rate\*

Outcome	Randomly Assigned Patients, n	Overall, n (%)	Enoxaparin Group, n (%)	Fondaparinux Group, n (%)	Hazard Ratio (95% CI)	P Value
<b>Death, MI, or refractory ischemia</b>						
9 d						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	363 (7.1)	191 (7.4)	172 (6.7)	0.90 (0.73–1.11)	0.32
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	297 (6.1)	140 (5.8)	157 (6.4)	1.10 (0.88–1.38)	0.41
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	235 (4.7)	116 (4.6)	119 (4.8)	1.03 (0.80–1.33)	0.81
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	252 (5.0)	123 (4.9)	129 (5.2)	1.05 (0.82–1.34)	0.70
Interaction	–	–	–	–	–	0.38
30 d						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	573 (11.1)	315 (12.2)	258 (10.0)	0.81 (0.69–0.96)	0.01
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	409 (8.4)	193 (8.1)	216 (8.8)	1.10 (0.90–1.33)	0.34
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	317 (6.3)	163 (6.5)	154 (6.2)	0.95 (0.76–1.18)	0.65
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	361 (7.2)	189 (7.6)	172 (6.9)	0.91 (0.74–1.12)	0.37
Interaction	–	–	–	–	–	0.45
180 d						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	946 (18.7)	495 (19.6)	451 (17.9)	0.90 (0.79–1.03)	0.12
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	603 (12.6)	297 (12.6)	306 (12.7)	1.01 (0.86–1.19)	0.87
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	467 (9.4)	245 (9.9)	222 (9.0)	0.91 (0.76–1.09)	0.30
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	503 (10.2)	265 (10.7)	238 (9.6)	0.90 (0.75–1.07)	0.22
Interaction	–	–	–	–	–	0.85
<b>Major bleeding events</b>						
9 d						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	233 (4.6)	163 (6.4)	70 (2.8)	0.42 (0.32–0.56)	<0.001
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	170 (3.5)	110 (4.6)	60 (2.5)	0.53 (0.39–0.72)	<0.001
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	123 (2.5)	74 (3.0)	49 (2.0)	0.66 (0.46–0.95)	0.026
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	103 (2.1)	64 (2.6)	39 (1.6)	0.61 (0.41–0.90)	0.014
Interaction	–	–	–	–	–	0.056
30 d						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	299 (5.9)	193 (7.6)	106 (4.2)	0.54 (0.42–0.68)	<0.001
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	209 (4.4)	127 (5.4)	82 (3.4)	0.62 (0.47–0.82)	<0.001
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	154 (3.1)	88 (3.5)	66 (2.7)	0.75 (0.55–1.03)	0.078
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	145 (2.9)	85 (3.4)	60 (2.4)	0.70 (0.50–0.98)	0.036
Interaction	–	–	–	–	–	0.093
180 d						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	359 (7.3)	216 (8.7)	143 (5.8)	0.65 (0.52–0.80)	<0.001
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	260 (5.5)	147 (6.3)	113 (4.8)	0.74 (0.58–0.95)	0.018
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	191 (3.9)	102 (4.1)	89 (3.6)	0.87 (0.66–1.16)	0.350
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	177 (3.6)	103 (4.2)	74 (3.0)	0.71 (0.53–0.96)	0.026
Interaction	–	–	–	–	–	0.301

\* GFR = glomerular filtration rate; MI = myocardial infarction.

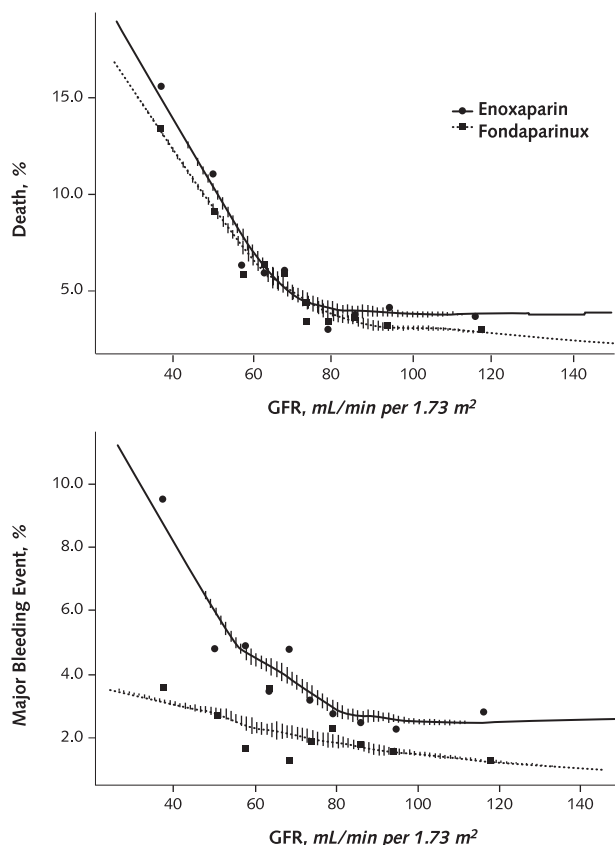
However, at 30 days among patients with a GFR less than 58 mL/min per 1.73 m<sup>2</sup>, the composite efficacy outcomes were statistically significantly lower with fondaparinux (10.0% vs. 12.2% with enoxaparin; hazard ratio, 0.81 [CI, 0.69 to 0.96]), as were the number of deaths alone (4.8% vs. 6.8%; hazard ratio, 0.69 [CI, 0.55 to 0.87]) (Appendix Table, Figure). Findings on number of deaths were similar when the results were expressed as a function of baseline creatinine level greater than 106 μmol/L (1.2 mg/dL): 4.5% for the fondaparinux group vs. 6.5% for the enoxaparin group (hazard ratio, 0.68 [CI, 0.54 to 0.86]).

A statistically significant difference in major bleeding events was observed in favor of fondaparinux (overall, 2.1% vs. 4.1% with enoxaparin; hazard ratio, 0.52 [CI,

0.44 to 0.61]). The rate of bleeding events was lower with fondaparinux across the quartiles of renal dysfunction, and the difference was most marked in patients with severe renal dysfunction (Figure, Table 2). In absolute terms, the rate of major bleeding was 1.0% to 3.6% lower with fondaparinux; hazard ratios for successive quartiles of renal dysfunction were 0.61 (CI, 0.41 to 0.90) for a GFR of at least 86 mL/min per 1.73 m<sup>2</sup>, 0.66 (CI, 0.46 to 0.95) for a GFR of 71 to less than 86 mL/min per 1.73 m<sup>2</sup>, 0.53 (CI, 0.39 to 0.72) for a GFR of 58 to less than 71 mL/min per 1.73 m<sup>2</sup>, and 0.42 (CI, 0.32 to 0.56) for a GFR less than 58 mL/min per 1.73 m<sup>2</sup>.

When the balance between efficacy and safety (the composite of death, MI, refractory angina or major bleeding), was considered event rates were lower at 9 days with

**Figure.** Relation between deaths and renal dysfunction by 180 days and between major bleeding events and renal dysfunction by 9 days.



Lines show smoothed estimates derived from individual data. Tick marks on the curves show the density of patients at each glomerular filtration rate (GFR).

fondaparinux than with enoxaparin (7.3% vs. 9.0%; hazard ratio, 0.81 [CI, 0.73 to 0.89]), and the difference was sustained at 180 days (15.0% vs 17.1%; hazard ratio, 0.86 [CI, 0.81 to 0.93]). Similarly, for each quartile of GFR, net clinical benefit at 180 days favored fondaparinux (hazard ratios, 0.83, 0.91, 0.88, and 0.86 for successive quartiles of renal dysfunction; tests for interaction were not significant) (Table 3). The absolute benefits in favor of fondaparinux were most marked and reached statistical significance only in patients with more severely impaired renal function (GFR <58 mL/min per 1.73 m<sup>2</sup>).

## DISCUSSION

A spectrum of renal dysfunction is evident in patients with coronary artery disease (1–7, 19). Only one quarter of patients presenting with non-ST-segment elevation ACS in this study had well-preserved renal function (GFR >86 mL/min per 1.73 m<sup>2</sup>), and one half had a GFR of less than 71 mL/min per 1.73 m<sup>2</sup>. Renal function was a powerful

and independent determinant of adverse outcome, including the risks for death and major and minor bleeding. Overall, the risk for death was approximately 5-fold higher in patients in the lowest quartile of renal dysfunction (GFR <58 mL/min per 1.73 m<sup>2</sup>) than in those with well-preserved renal function (GFR >86 mL/min per 1.73 m<sup>2</sup>). Similarly, the risk for major bleeding was 4-fold higher among those in the lowest versus the highest quartiles of GFR.

The rate of major bleeding was approximately 2-fold higher with enoxaparin than with fondaparinux: 2.1% vs. 4.1% (hazard ratio, 0.52 [CI, 0.44 to 0.61]). The relationship between bleeding and renal dysfunction demonstrates a substantial increase in risk for bleeding in patients with the most marked impairment of renal function (GFR <58 mL/min per 1.73 m<sup>2</sup>): 6.4% with enoxaparin versus 2.8% with fondaparinux, respectively) hazard ratio, 0.42 [CI, 0.32 to 0.56]). Examining patients by quartile of GFR or plotting the results over the spectrum of GFR demonstrates that not only are bleeding risks amplified as renal dysfunction deteriorates, but the difference between fondaparinux and enoxaparin progressively widens.

A possible explanation for our findings is that clearance of enoxaparin may be impaired in patients with impaired renal function when the drug is administered in the standard dosing regimen, and this impaired clearance is associated with excess bleeding. Clearance of enoxaparin involves metabolism by desulfation or depolymerization to lower-molecular-weight species, and renal clearance of active and inactive fragments. In contrast, fondaparinux is excreted by the kidney without previous metabolism. In the context of thrombolytic therapy for ST-segment elevation MI, higher bleeding risks were observed with enoxaparin, especially in elderly persons (20–22). These results may relate, at least in part, to impaired renal function.

Excessive bleeding may translate into subsequent risk for death by several mechanisms, including the withdrawal of antiplatelet and antithrombotic agents in patients who experience a bleeding event (with rebound thrombosis and death arising from ischemic complications). Bleeding event are also associated with transfusions, the hazards of which have been well documented, including in large observational studies on ACS (4,5, 23). Finally, bleeding may occur into vulnerable atherosclerotic plaques, contributing to vascular obstruction and potentially to a higher frequency of death.

In the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment trial, which studied ST-segment elevation MI, the dose of enoxaparin was reduced in elderly patients (to 75% of the standard dose in patients >75 years of age) and was also reduced in those with severe renal dysfunction (creatinine clearance <0.5 mL/s [30 mL/min]) (22). Despite this dose reduction, there was significant excess bleeding with enoxaparin compared with unfractionated heparin (2.1% vs. 1.4%; *P* < 0.001). These findings, together with those of OASIS 5,

Table 3. Rates of the Composite Outcome at 9, 30, and 180 days, by Glomerular Filtration Rate\*

Time Point	Randomly Assigned Patients, n	Overall, n (%)	Enoxaparin Group, n (%)	Fondaparinux Group, n (%)	Hazard Ratio (95% CI)†	P Value
<b>9 d</b>						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	546 (10.6)	321 (12.5)	225 (8.8)	0.69 (0.58–0.82)	<0.001
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	428 (8.8)	230 (9.6)	198 (8.1)	0.84 (0.69–1.01)	0.066
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	334 (6.7)	177 (7.1)	157 (6.3)	0.89 (0.72–1.10)	0.28
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	330 (6.6)	174 (7.0)	156 (6.2)	0.89 (0.72–1.11)	0.31
Interaction	–	–	–	–	–	0.04
<b>30 d</b>						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	786 (15.3)	454 (17.6)	332 (12.9)	0.71 (0.62–0.82)	<0.001
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	567 (11.7)	295 (12.3)	272 (11.1)	0.89 (0.76–1.05)	0.18
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	436 (8.7)	233 (9.3)	203 (8.1)	0.87 (0.72–1.05)	0.15
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	466 (9.3)	252 (10.1)	214 (8.6)	0.85 (0.70–1.01)	0.07
Interaction	–	–	–	–	–	0.12
<b>180 d</b>						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	1164 (23.0)	628 (24.7)	536 (21.3)	0.83 (0.74–0.93)	0.001
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	782 (16.3)	404 (17.0)	378 (15.6)	0.91 (0.79–1.04)	0.17
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	610 (12.3)	324 (13.1)	286 (11.5)	0.88 (0.75–1.03)	0.12
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	626 (12.7)	336 (13.6)	290 (11.7)	0.86 (0.73–1.00)	0.053
Interaction	–	–	–	–	–	0.70

\* The composite outcome was death, myocardial infarction, refractory ischemia, and major bleeding.

† Kaplan–Meier and Cox proportional hazards ratios.

suggest that a more systematic dose adjustment of enoxaparin may be required across the spectrum of renal dysfunction in patients with ACS. A meta-analysis of low-molecular-weight heparins in renal dysfunction (trials in ACS and venous thromboembolism) suggested that enoxaparin results in a 2- to 3-fold increase in major bleeding events when creatinine clearance is less than 0.5 mL/s (<30 mL/min) and may cause more bleeding than other low-molecular-weight heparins (24). Trials with empirical dose adjustment, whether based on creatinine clearance or guided by anti-factor Xa levels, appeared to show lower bleeding rates (24). The pharmacologic properties, bioavailability, and specificity of fondaparinux and low-molecular-weight heparins differ (25, 26). These features of fondaparinux, together with the lack of binding to endothelial cells and plasma proteins and the lack of direct antithrombin activity, may minimize interpatient variability and reduce bleeding (25, 26).

Half of the patients presenting with non–ST-segment elevation ACS have a GFR less than 54 mL/min per 1.73 m<sup>2</sup>; hence, dose adjustment of antithrombotics may be required in a substantial proportion of patients. The association between bleeding and deaths suggests that every effort is needed in future studies to minimize the risks for major bleeding. In the absence of dose adjustment, fondaparinux is associated with lower risk for bleeding at all levels of renal function.

Although the results of our subgroup analysis must be interpreted with caution, these data suggest that the choice of therapy for non–ST-segment elevation ACS needs to take into account not only the effect on preventing isch-

emic events but also the effect on bleeding. Bleeding may influence longer-term mortality. The balance between efficacy and safety differs across the spectrum of renal dysfunction, and the findings of OASIS 5 suggest that compared with the currently approved regimen of enoxaparin, fondaparinux has a lower risk for bleeding events and a significant advantage in risks for death. The powerful association between renal dysfunction and the adverse outcomes of death and of bleeding suggests that results from patients with well-preserved renal function should not be extrapolated to the full spectrum of patients presenting with non–ST-segment elevation ACS.

From the University of Edinburgh, Edinburgh, United Kingdom; McMaster Clinic, Hamilton, Ontario, Canada; University Hospital Jean-Minjoz, Besançon, France; Montreal Heart Institute, Montréal, Québec, Canada; Uppsala University Hospital, Uppsala, Sweden; Instituto Dante Pazzanese, São Paulo, Brazil; and Hospital Clinico Universitario, Valencia, Italy.

**Potential Financial Conflicts of Interest:** *Consultancies:* K.A.A. Fox, J.P. Bassand, S.R. Mehta (GlaxoSmithKline, Eli Lilly Inc., Sanofi-Aventis), S. Yusuf (GlaxoSmithKline, Sanofi-Aventis). *Honoraria:* K.A.A. Fox, J.P. Bassand, S. Yusuf (GlaxoSmithKline, Sanofi-Aventis). *Grants received:* K.A.A. Fox (for OASIS 5), S.R. Mehta (Population Health Research Institute, from Glaxo SmithKline and Sanofi-Aventis), S. Yusuf (GlaxoSmithKline, Sanofi-Aventis). *Grants pending:* S. Yusuf (Sanofi-Aventis).

**Requests for Single Reprints:** Keith A.A. Fox, MBChB, Cardiovascular Research, The University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, United Kingdom; e-mail, k.a.a.fox@ed.ac.uk.

Current author addresses and author contributions are available at [www.annals.org](http://www.annals.org).

## References

1. Beattie JN, Soman SS, Sandberg KR, Yee J, Borzak S, Garg M, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis*. 2001;37:1191-200. [PMID: 11382688]
2. Freeman RV, Mehta RH, Al Badr W, Cooper JV, Kline-Rogers E, Eagle KA. Influence of concurrent renal dysfunction on outcomes of patients with acute coronary syndromes and implications of the use of glycoprotein IIb/IIIa inhibitors. *J Am Coll Cardiol*. 2003;41:718-24. [PMID: 12628712]
3. GRACE Investigators. Creatinine clearance and adverse hospital outcomes in patients with acute coronary syndromes: findings from the global registry of acute coronary events (GRACE). *Heart*. 2003;89:1003-8. [PMID: 12923009]
4. Moscucci M, Fox KA, Cannon CP, Klein W, López-Sendón J, Montalescot G, et al. Predictors of major bleeding in acute coronary syndromes: the Global Registry of Acute Coronary Events (GRACE). *Eur Heart J*. 2003;24:1815-23. [PMID: 14563340]
5. Krumholz HM, Chen J, Wang Y, Radford MJ, Chen YT, Marciniak TA. Comparing AMI mortality among hospitals in patients 65 years of age and older: evaluating methods of risk adjustment. *Circulation*. 1999;99:2986-92. [PMID: 10368115]
6. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med*. 2004;351:1285-95. [PMID: 15385655]
7. Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke*. 1997;28:557-63. [PMID: 9056611]
8. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C, et al. Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA*. 2005;293:1737-45. [PMID: 15827312]
9. Culleton BF, Larson MG, Wilson PW, Evans JC, Parfrey PS, Levy D. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int*. 1999;56:2214-9. [PMID: 10594797]
10. Yerkey MW, Kernis SJ, Franklin BA, Sandberg KR, McCullough PA. Renal dysfunction and acceleration of coronary disease. *Heart*. 2004;90:961-6. [PMID: 15253986]
11. GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291:2727-33. [PMID: 15187054]
12. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation*. 2005;112:3855-67. [PMID: 16344381]
13. SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: primary results of the SYNERGY randomized trial. *JAMA*. 2004;292:45-54. [PMID: 15238590]
14. STEEPLE Investigators. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med*. 2006;355:1006-17. [PMID: 16957147]
15. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. *N Engl J Med*. 2006;354:1464-76. [PMID: 16537663]
16. MICHELANGELO OASIS 5 Steering Committee. Design and rationale of the MICHELANGELO Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial program evaluating fondaparinux, a synthetic factor Xa inhibitor, in patients with non-ST-segment elevation acute coronary syndromes. *Am Heart J*. 2005;150:1107. [PMID: 16338245]
17. Fadem SZ. The Modification of Diet in Renal Disease (MDRD) GFR Calculator. Nephron Information Center; 2000. Accessed at [www.kidney.org/professionals/KDOQI/gfr\\_calculator.cfm](http://www.kidney.org/professionals/KDOQI/gfr_calculator.cfm) on 14 June 2007.
18. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145:247-54. [PMID: 16908915]
19. Jernberg T, Lindahl B, James S, Larsson A, Hansson LO, Wallentin L. Cystatin C: a novel predictor of outcome in suspected or confirmed non-ST-elevation acute coronary syndrome. *Circulation*. 2004;110:2342-8. [PMID: 15477399]
20. Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605-13. [PMID: 11530146]
21. Wallentin L, Goldstein P, Armstrong PW, Granger CB, Adgey AA, Arntz HR, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation*. 2003;108:135-42. [PMID: 12847070]
22. ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354:1477-88. [PMID: 16537665]
23. CRUSADE Investigators. Excess dosing of antiplatelet and antithrombin agents in the treatment of non-ST-segment elevation acute coronary syndromes. *JAMA*. 2005;294:3108-16. [PMID: 16380591]
24. Lim W, Dentali F, Eikelboom JW, Crowther MA. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144:673-84. [PMID: 16670137]
25. Weitz JI. New anticoagulants for treatment of venous thromboembolism. *Circulation*. 2004;110:119-26. [PMID: 15339877]
26. Hirsh J, O'Donnell M, Weitz JI. New anticoagulants. *Blood*. 2005;105:453-63. [PMID: 15191946]

**Current Author Addresses:** Dr. Fox: Cardiovascular Research, The University of Edinburgh, Chancellor's Building, 49 Little France Crescent, Edinburgh EH16 4SB, United Kingdom.

Dr. Bassand: Department of Cardiology, Pôle Coeur Poumons, University Hospital Jean-Minjoz, Boulevard Fleming, 25030 Besançon Cedex, France.

Dr. Mehta: Hamilton Health Sciences, General Division, McMaster Clinic, 237 Barton Street East Hamilton, Ontario L8L 2X2, Canada.

Dr. Wallentin: Uppsala University Hospital, UCR, 75185 Uppsala, Sweden.

Dr. Theroux: Montreal Heart Institute, 5000 Belanger East, Montréal, Québec H1T 1C8, Canada.

Dr. Soares Piegas: Instituto Dante Pazzanese de Cardiologia, Avenida Dr. Dante Pazzanese 500-12 andar, CEP 04012-80, São Paulo, Brazil.

Dr. Valentin: Unidad Coronaria, Hospital Universitaria Dr. Peset, Valencia, Spain.

Dr. Moccetti: Cardiocentro Ticino, Lugano, Italy.

Ms. Chrolavicius and Mr. Afzal: Population Health Research Institute, HHSC, Hamilton General Hospital, McMaster Clinic, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.

Dr. Yusuf: Department of Medicine (Cardiology), HHSC, Hamilton General Hospital, McMaster Clinic, 237 Barton Street East, Hamilton, Ontario L8L 2X2, Canada.

**Author Contributions:** Conception and design: K.A.A. Fox, S.R. Mehta, L. Wallentin, P. Theroux, V. Valentin, S. Chrolavicius.

Analysis and interpretation of the data: K.A.A. Fox, S.R. Mehta, L. Wallentin, V. Valentin, S. Chrolavicius, R. Afzal.

Drafting of the article: K.A.A. Fox, J.P. Bassand, L. Wallentin, V. Valentin.

Critical revision of the article for important intellectual content: K.A.A. Fox, J.P. Bassand, S.R. Mehta, L. Wallentin, P. Theroux, V. Valentin, R. Afzal.

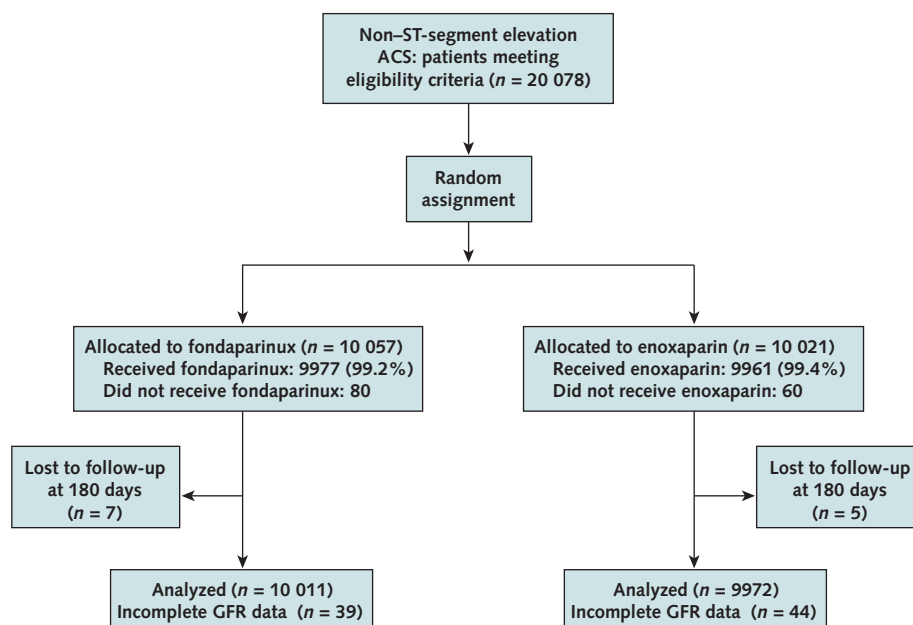
Final approval of the article: K.A.A. Fox, J.P. Bassand, L. Wallentin, P. Theroux, V. Valentin.

Provision of study materials or patients: L. Wallentin, V. Valentin.

Statistical expertise: P. Theroux, R. Afzal.

Collection and assembly of data: V. Valentin, S. Chrolavicius.

Appendix Figure. Study flow diagram.



ACS = acute coronary syndromes; GFR = glomerular filtration rate.

**Appendix Table. Deaths at 9, 30, and 180 Days, by Glomerular Filtration Rate\***

Time Point	Randomly Assigned Patients, n	Overall, n (%)	Enoxaparin Group, n (%)	Fondaparinux Group, n (%)	Hazard Ratio (95% CI)†	P Value
<b>9 d</b>						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	169 (3.3)	93 (3.6)	76 (3.0)	0.82 (0.60–1.11)	0.19
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	101 (2.1)	50 (2.1)	51 (2.1)	1.00 (0.68–1.47)	0.99
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	51 (1.0)	19 (0.8)	32 (1.3)	1.70 (0.96–2.99)	0.07
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	40 (0.8)	23 (0.9)	17 (0.7)	0.74 (0.39–1.38)	0.35
Interaction	–	–	–	–	–	0.37
<b>30 d</b>						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	299 (5.8)	176 (6.8)	123 (4.8)	0.69 (0.55–0.87)	<0.002
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	159 (3.3)	75 (3.1)	84 (3.4)	1.10 (0.80–1.50)	0.57
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	92 (1.8)	43 (1.7)	49 (2.0)	1.15 (0.76–1.73)	0.51
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	93 (1.9)	56 (2.2)	37 (1.5)	0.66 (0.44–1.00)	0.049
Interaction	–	–	–	–	–	0.44
<b>180 d</b>						
GFR <58 mL/min per 1.73 m <sup>2</sup>	5141	563 (11.2)	303 (12.0)	260 (10.4)	0.85 (0.72–1.00)	0.056
GFR 58 to <71 mL/min per 1.73 m <sup>2</sup>	4845	286 (6.0)	140 (6.0)	146 (6.1)	1.02 (0.81–1.29)	0.84
GFR 71 to <86 mL/min per 1.73 m <sup>2</sup>	5012	178 (3.6)	90 (3.7)	88 (3.6)	0.98 (0.73–1.32)	0.92
GFR ≥86 mL/min per 1.73 m <sup>2</sup>	4996	180 (3.7)	102 (4.2)	78 (3.2)	0.76 (0.57–1.02)	0.069
Interaction	–	–	–	–	–	0.87

\* GFR = glomerular filtration rate.

† Kaplan–Meier and Cox proportional hazards ratios.