Original Investigation

# Association Between the Use of Fondaparinux vs Low-Molecular-Weight Heparin and Clinical Outcomes in Patients With Non–ST-Segment Elevation Myocardial Infarction

Karolina Szummer, MD, PhD; Jonas Oldgren, MD, PhD; Lars Lindhagen, PhD; Juan Jesus Carrero, PhD; Marie Evans, MD, PhD; Jonas Spaak, MD, PhD; Robert Edfors, MD; Stefan H Jacobson, MD, PhD; Pontus Andell, MD; Lars Wallentin, MD, PhD; Tomas Jernberg, MD, PhD

**IMPORTANCE** Fondaparinux was associated with reduced major bleeding events and improved survival compared with low-molecular-weight heparin (LMWH) in a large randomized clinical trial involving patients with non–ST-segment elevation myocardial infarction (NSTEMI). Large-scale experience of the use of fondaparinux vs LMWH in a nontrial setting is lacking.

**OBJECTIVE** To study the association between the use of fondaparinux vs LMWH and outcomes in patients with NSTEMI in Sweden.

**DESIGN, SETTING, AND PATIENTS** Prospective multicenter cohort study from the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies registry involving 40 616 consecutive patients with NSTEMI who received fondaparinux or LMWH between September 1, 2006, through June 30, 2010, with the last follow-up on December 31, 2010.

**EXPOSURES** In-hospital treatment with fondaparinux or LMWH during the hospital stay.

**MAIN OUTCOMES AND MEASURES** In-hospital severe bleeding events and death and 30- and 180-day death, MI, stroke, and major bleeding events. Logistic regression models adjusted for calendar time, admitting hospital, baseline characteristics, and in-hospital revascularization.

**RESULTS** In total, 14 791 patients (36.4%) were treated with fondaparinux and 25 825 (63.6%) with LMWH. One hundred sixty-five patients (1.1%) in the fondaparinux group vs 461 patients (1.8%) in the LMWH group experienced in-hospital bleeding events (adjusted odds ratio [OR], 0.54; 95% CI, 0.42-0.70). A total of 394 patients (2.7%) in the fondaparinux group died while in the hospital vs 1022 (4.0%) in the LMWH group (adjusted OR, 0.75; 95% CI, 0.63-0.89). The differences in major bleeding events and mortality between the 2 treatments were similar at 30 and 180 days. There were no significant differences in the number of recurrent MI and stroke events at 30 or 180 days among the 2 treatment groups.

**CONCLUSIONS AND RELEVANCE** In routine clinical care of patients with NSTEMI, fondaparinux was associated with lower odds than LMWH of major bleeding events and death both in-hospital and up to 180 days afterward.

Supplemental content at jama.com

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Karolina Szummer, MD, PhD, Department of Cardiology, Karolinska University Hospital, Department of Medicine, Huddinge; Karolinska Institutet; 141 86 Stockholm, Sweden (karolina.szummer@karolinska.se).

*JAMA*. 2015;313(7):707-716. doi:10.1001/jama.2015.517

The development of new therapies for acute coronary syndromes is usually focused on reducing ischemic outcomes, while maintaining similar safety regarding bleeding events. Reducing bleeding events in patients receiving antithrombotic therapy is important since bleeding events are associated with increased mortality.[1] In patients with a non-ST-segment elevation myocardial infarction (NSTEMI), the factor Xa inhibitor fondaparinux was noninferior to the low-molecular-weight heparin (LMWH) enoxaparin in reducing ischemic outcomes in the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5)[2] study. However, fondaparinux treatment reduced severe in-hospital bleeding events, which translated into both short- and long-term reduction in mortality.

**CABG** *coronary artery bypass graft*

**eGFR** *estimated glomerular filtration rate*

**LMWH** *low-molecular-weight heparin*

**MI** *myocardial infarction*

**NSTEMI** *non–ST-segment elevation myocardial infarction*

**PCI** *percutaneous coronary intervention*

Two subgroups of patients have received special attention and separate post hoc analysis of the main OASIS-5 trial: patients with renal dysfunction and patients undergoing percutaneous coronary intervention (PCI) during the hospitalization. Despite a higher risk of bleeding among patients with reduced renal function,[3] the reduction in bleeding events was largest in patients with moderately reduced renal function treated with fondaparinux compared with LMWH.[4] In patients who underwent PCI, the outcomes were consistent with the main OASIS-5 trial results,[5] even though there was an increased rate of thrombus formation on the angioplasty material among patients who received fondaparinux compared with those who received LMWH.

After the European Society of Cardiology[6] and the Swedish National Board of Health and Welfare recommended fondaparinux as the first-choice anticoagulant to treat patients with NSTEMI, there was a rapid switch from LMWH to fondaparinux in the routine care of patients in Sweden. The aim of this study was to assess the rate of ischemic and bleeding events among a wide range of nonselected, nontrial patients with NSTEMI who were treated with either fondaparinux or LMWH. We also specifically aimed to assess the association between the 2 anticoagulants and outcome in patients with reduced renal function and in patients undergoing PCI.

## Methods

### Registry, Patient Selection, and Merging With Other Registries

The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry[7] was used for patient selection. The registry is nationwide and includes all consecutive patients admitted to a coronary care unit with symptoms suggestive of an acute coronary syndrome. Currently, all 72 Swedish hospitals that provide care for acute cardiac diseases participate in the registry. More than 100 variables regarding baseline characteristics, medication on admission, in-hospital therapies, complications, and discharge medication are collected (http://www.ucr.uu.se/swedeheart/). A monitor evaluates the correctness of data entered in the registry with the medical records yearly (agreement is around 96%).

In this study, consecutive patients older than 18 years who had NSTEMI that had been registered for the first time and who were treated with either fondaparinux or LMWH between September 1, 2006, and June 30, 2010, were selected. The last follow-up was on December 31, 2010. The OASIS-5 trial was published on March 16, 2006. The European Medicines Agency approved fondaparinux August 29, 2007.

Data on baseline characteristics were enriched with information from the National Patient Registry, which includes the diagnoses of all hospital admissions in Sweden since 1987. The National Board of Health and Welfare approved the merge between these registries. Patients do not provide written consent, but are informed about their participation in the registry and are allowed to opt-out. The study protocol was approved by the regional ethics committee in Stockholm.

### Outcome Definitions

The outcome measures in this study were in-hospital severe bleeding events and death and 30- and 180-day major bleeding, death, stroke, and recurrent myocardial infarction (MI). An in-hospital severe bleeding event was registered as a complication by the treating physician in the SWEDEHEART registry and consisted of fatal, cerebral, or bleeding requiring transfusion or surgery. Data on 30- and 180-day outcomes regarding readmission due to MI, stroke, or major bleeding events were based on *International Statistical Classification of Diseases, Tenth Revision (ICD-10)* codes from the National Patient Registry (eTable 1 in the Supplement). Death dates were obtained from the Swedish population registry.

### Renal Function and Categories

Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine measurements at the time of admission, sex, and age using the Chronic Kidney Disease Epidemiology Collaboration equation.[8] The majority of creatinine assessments from 61 of 72 hospitals were performed by either enzymatic or corrected Jaffe method (alkaline picrate reaction), which both are traceable to isotope dilution mass spectroscopy standards. For creatinine measurements performed with nontraceable methods, values were reduced by 5% prior to being entered into the equation formula.[9-11] The current Kidney Disease Improving Global Outcomes classification was used to define 5 renal function categories according to eGFR (mL/min/1.73 $m^2$).[11] In the absence of data on albuminuria, these can only be considered renal function strata and not chronic kidney disease stages.

### Statistical Analysis

Baseline characteristics are described as median (interquartile range [IQR]) for continuous variables or as a percentage for categorical variables. Logistic regression was used to estimate the odds ratio (OR) and 95% CI for having an event at each

time point for patients treated with fondaparinux compared with those treated with LMWH (**Table 1**). The relation between treatment, confounders, and the outcome is described as a directed acyclic graph (eFigure 1 in the Supplement). The purpose of the directed acyclic graph is to graphically represent the factors that may have a causal effect on the outcome and their relation to one another. This representation is then used to choose which confounders should be included in the adjusted models. Because the replacement of LMWH with fondaparinux resulted mainly to changes in national and local guidelines, adjustments were made initially for only calendar time (4-knot-restricted cubic spline) and hospital site. Because baseline characteristics differed between the treatment groups, additional adjustments for baseline characteristics were performed (main model), including the increasing use of revascularization over the study period. Thus, adjustments for covariates were performed in a stepwise fashion. Model 1 included hospital (random effect) and calendar time. Model 2, the main model, included model 1 and baseline characteristics—age (3-knot-restricted cubic spline); sex; current smoking status; diagnosis of diabetes; hypertension; previous MI, congestive heart failure, peripheral vascular disease, ischemic stroke, bleeding, chronic obstructive pulmonary disease, or cancer; Killip score greater than 1; and eGFR. Model 3 included model 2 and in-hospital revascularization therapy (PCI or coronary artery bypass graft [CABG] surgery).

The models stratified for renal function stage were adjusted as in the main analyses. The association between treatment and outcome in the different renal function strata were tested for linear trend (2-sided *P* value for trend, with $P < .05$ considered significant).

The association between treatment regimen and outcome was also studied in patients undergoing PCI during the index hospitalization. The PCI data were adjusted in accordance with models 1 and 2, and then for PCI-specific variables (use of unfractionated heparin; LMWH; bivalirudin; glycoprotein IIb/IIIa receptor blockers during PCI; the access vessel; use of closure device; and time from arrival to the coronary care unit to PCI in categories of 0, 1, 2, or ≥3 days).

Missing data were imputed 3 times using multiple imputations with the method of chained equation.[12] Current smoking status had the most missing values of the (8.8% of all patients). All applicable variables that were used as covariates in the models and all outcome variables were used to predict the value of the missing covariate.

Three sensitivity analyses were performed (eTable 2 in the Supplement). The first was a complete case analysis done on patients with complete data on all covariates (n = 35 427) with adjustments as in the model 2.

The second sensitivity analysis was a propensity-score matched analysis with exact matching on calendar-time (quarters) and in-hospital PCI. First, the propensity scores were estimated using logistic regression models with fondaparinux as outcome and all variables of the main model (model 2 above) as explanatory variables, except for in-hospital anticoagulants (outcome), calendar time, and PCI. Hospital site was added as a random effect. In the next step, patients were matched on estimated propensity scores using a combination of exact and full matching.[13] The matching was exact concerning calendar quarter and in-hospital PCI. Full matching means that a patient treated with fondaparinux could be matched to several patients treated with LMWH and vice versa. The caliper (upper limit to the allowed difference in propensity score between matched patients treated with LMWH and fondaparinux) was 0.002 (except for eGFR >15-30, for which the caliper was 0.005, and eGFR ≤15, for which the caliper was 0.01). Unmatched patients were removed in the subsequent analysis. The effective number of matched pairs was much smaller than the total number of patients available for matching (details of the analysis are presented in eTable 3 in the Supplement). The PCI subgroup had only patients with eGFR greater than 30 available for matching. Finally, the actual analysis was performed as a logistic regression with in-hospital anticoagulants as a predictor and the matching indicator as a random effect. Each such analysis (prediction of propensity scores, matching, and logistic regression) was repeated for each imputed data set.

The third sensitivity analysis was based on first-time MI included (excluding all patients with previous MI) in the registry. Use of first-time registration (used in the main analysis) included in a nationwide cohort of patients could cause a bias with a higher prevalence of older patients who would likely have more comorbidities in the earlier period than in the later period.

All analyses were performed with R (version 3.1.0, R packages lme4, mice, optmatch).

## Results

A total of 40 616 patients with NSTEMI were treated with either fondaparinux or LMWH from September 1, 2006, through June 30, 2010. The use of fondaparinux increased from 0.7% in the first calendar year to 84.8% in the last calendar year (**Figure 1**). Overall, 14 791 patients (36.4%) received fondaparinux and 25 825 (63.6%) received LMWH.

Patients who were treated with fondaparinux were a mean 2 years younger (72 years vs 74 years) than those treated with LMWH, had fewer previous MIs (28.2% vs 32.2%), and fewer had been previously diagnosed with congestive heart failure (14.5% vs 18.7%). The rate of prior bleeding events and previous hemorrhagic stroke was similar between both groups (Table 1). In-hospital therapies differed with more patients having undergone PCI (46.4% vs 38.9%) in the fondaparinux group than in the LMWH group.

### Bleeding Events and Mortality

The absolute rate of severe in-hospital bleeding events was lower in fondaparinux group than the LMWH group (1.1% vs 1.8%), and the adjusted odds of bleeding events were lower (OR, 0.54; 95% CI, 0.42-0.70; **Table 2**). The mortality rate among patients who had a severe in-hospital bleeding event was similar between groups: 19 patients (11.5%) of 165 in the fondaparinux group and 54 patients (11.7%) of 461 in the LMWH group. The rate of severe bleeding while in the hospital or causing readmission was similarly lower in the fondaparinux group

Table 1. Baseline Characteristics

| | No. (%) of Patients | | |
|---|---|---|---|
| | All (N = 40 616) | Fondaparinux (n = 14 791) | LMWH (n = 25 825) |
| Age, median (IQR), y | 73 (63-81) | 72 (62-81) | 74 (63-82) |
| Women | 15 108 (37.2) | 5392 (36.5) | 9716 (37.6) |
| Diabetes | 10 707 (26.4) | 3752 (25.4) | 6955 (26.9) |
| Hypertension | 22 643 (55.7) | 8363 (56.5) | 14 280 (55.3) |
| Current smoking status | 7548 (20.4) | 2848 (21.0) | 4700 (20.0) |
| Previous medical events | | | |
| Myocardial infarction | 12 479 (30.7) | 4166 (28.2) | 8313 (32.2) |
| PCI | 5548 (13.7) | 2132 (14.4) | 3416 (13.2) |
| CABG surgery | 4183 (10.3) | 1508 (10.2) | 2675 (10.4) |
| Congestive heart failure | 6975 (17.2) | 2149 (14.5) | 4826 (18.7) |
| Peripheral vascular disease | 2678 (6.6) | 890 (6.0) | 1788 (6.9) |
| Ischemic stroke | 4574 (11.3) | 1499 (10.1) | 3075 (11.9) |
| Hemorrhagic stroke | 549 (1.4) | 204 (1.4) | 345 (1.3) |
| Bleeding | 2467 (6.1) | 902 (6.1) | 1565 (6.1) |
| Chronic obstructive pulmonary disease | 4420 (10.9) | 1638 (11.1) | 2782 (10.8) |
| Cancer within last 3 y | 1196 (2.9) | 435 (2.9) | 761 (2.9) |
| Killip classification >1 on admission | 6162 (15.8) | 1792 (12.7) | 4370 (17.6) |
| Medication at admission | | | |
| Aspirin | 19 765 (48.7) | 6874 (46.5) | 12 891 (49.9) |
| Dual antiplatelet therapy | 2561 (6.3) | 896 (6.1) | 1665 (6.5) |
| β-Blocker | 17 557 (43.3) | 6128 (41.5) | 11 429 (44.3) |
| Calcium antagonist | 7618 (18.8) | 2820 (19.1) | 4798 (18.6) |
| Digoxin | 1056 (2.6) | 309 (2.1) | 747 (2.9) |
| ACE/ARB inhibitors | 14 469 (35.7) | 5401 (36.5) | 9068 (35.1) |
| Diuretic | 12 440 (30.7) | 4065 (27.5) | 8375 (32.5) |
| Statin | 12 857 (31.7) | 4833 (32.7) | 8024 (31.1) |
| In-hospital revascularization | | | |
| PCI | 16 901 (41.6) | 6858 (46.4) | 10 043 (38.9) |
| Days to PCI | | | |
| 0 | 2735 (16.2) | 988 (14.4) | 1747 (17.4) |
| 1 | 4818 (28.5) | 2073 (30.2) | 2745 (27.4) |
| 2 | 2389 (19.5) | 1426 (20.8) | 1863 (18.6) |
| ≥3 | 6041 (35.8) | 2366 (34.5) | 3675 (36.6) |
| PCI-adjunctive therapy, % per patient | | | |
| Unfractionated heparin | 11 529 (68.8) | 5271 (77.6) | 6258 (62.7) |
| LMWH at PCI | 888 (5.3) | 174 (2.6) | 714 (7.2) |
| Bivalirudin | 3030 (18.1) | 1507 (22.2) | 1523 (15.3) |
| Glycoprotein IIb/IIIa blocker | 3169 (18.9) | 822 (12.1) | 2347 (23.5) |
| Femoral access vessel | 10 073 (59.7) | 3673 (53.7) | 6400 (63.8) |
| Radial access vessel | 6802 (40.3) | 3173 (46.3) | 3629 (36.2) |
| Closure device | 5095 (30.2) | 2262 (33.1) | 2833 (28.3) |
| CABG | 1158 (2.9) | 475 (3.2) | 683 (2.6) |
| Intravenous therapies | | | |
| Inotropes | 856 (2.1) | 213 (1.4) | 643 (2.5) |
| Diuretic | 9611 (23.7) | 2883 (19.5) | 6728 (26.1) |
| In-hospital findings | | | |
| LVEF <50% | 11 153 (40.8) | 3871 (36.7) | 7282 (43.4) |
| New atrial fibrillation | 1522 (3.8) | 450 (3.1) | 1072 (4.3) |

(continued)

Table 1. Baseline Characteristics (continued)

| | No. (%) of Patients | | |
|---|---|---|---|
| | All (N = 40 616) | Fondaparinux (n = 14 791) | LMWH (n = 25 825) |
| Medication at discharge | | | |
| Aspirin | 37 531 (95.8) | 13 908 (96.6) | 23 623 (95.3) |
| Dual antiplatelet therapy | 28174 (71.9) | 11 232 (78.0) | 16 942 (68.3) |
| β-Blocker | 34 896 (89.0) | 12 893 (89.6) | 22 003 (88.7) |
| Calcium antagonist | 7142 (18.2) | 2732 (19.0) | 4410 (17.8) |
| Digoxin | 1114 (2.8) | 318 (2.2) | 796 (3.2) |
| ACE/ARB inhibitor | 26 570 (67.8) | 10 460 (72.7) | 16 110 (65.0) |
| Diuretic | 14 359 (36.6) | 4612 (32.0) | 9747 (39.3) |
| Statin | 32 252 (82.3) | 12 497 (86.9) | 19 755 (79.7) |
| PCI available at hospital | 24 672 (60.7) | 9504 (64.3) | 15 168 (58.7) |
| Serum creatinine, mg/dL | | | |
| Median (IQR) | 1.0 (0.8-1.2) | 0.9 (08-1.1) | 1.0 (0.8-1.2) |
| >3.0 mg/dL | 730 (1.8) | 149 (1.0) | 581 (2.2) |
| eGFR, CKD-EPI, median (IQR), mL/min/1.73 $m^2$ | 72.1 (52.9-87.8) | 74.3 (56.3-88.8) | 70.7 (51.0-87.0) |
| >90 | 8621 (21.2) | 3379 (22.8) | 5242 (20.3) |
| >60-90 | 18 487 (45.5) | 7057 (47.7) | 11 430 (44.3) |
| >30-60 | 10 922 (26.9) | 3718 (25.1) | 7204 (27.9) |
| >15-30 | 2009 (4.9) | 522 (3.5) | 1487 (5.8) |
| ≤15 | 577 (1.4) | 115 (0.8) | 462 (1.8) |

Abbreviations: ACE/ARB, angiotensin-converting enzyme/angiotensin II receptor blocker; CABG, coronary artery bypass graft; CKD-EPI, chronic kidney disease epidemiology equation; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LMWH, low-molecular-weight heparin; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

SI conversion factor: to convert creatinine from mg/dL to μmol/L, multiply by 88.4.

both at 30 days (1.4% vs 2.1%; adjusted OR, 0.56; 95% CI, 0.44-0.70) and at 180 days (1.9% vs 2.8%, adjusted OR, 0.60; 95% CI, 0.50-0.74). Patients in the fondaparinux group had lower adjusted odds of having either a severe bleeding or death event in the hospital (OR, 0.68; 95% CI, 0.58-0.79), at 30 days (OR, 0.74; 95% CI, 0.65-0.84), and at 180 days (OR, 0.72; 95% CI, 0.65-0.80) than patients in the LMWH group (Table 2).

In-hospital mortality was lower in the fondaparinux group than in the LMWH group (2.7% vs 4.0%; adjusted OR, 0.75; 95% CI, 0.63-0.89). Similarly lower adjusted ORs were observed at 30 days (OR, 0.82; 95% CI, 0.71-0.95) and at 180 days (OR, 0.76; 95% CI, 0.68-0.85; Table 2).

## Recurrent MI and Stroke

The rate of recurrent MI in the fondaparinux group was 9.0% vs 9.5% in the LMWH group at 30 days (adjusted OR, 0.94; 95% CI, 0.84-1.06) and was 14.2% vs 15.8% at 180 days (adjusted OR, 0.97; 95% CI, 0.89-1.06). The rate of stroke was low in both groups and did not differ in ORs after adjustments at 30 days (OR, 1.11; 95% CI, 0.74-1.65) and at 180 days (OR, 0.98; 95% CI, 0.79-1.22).

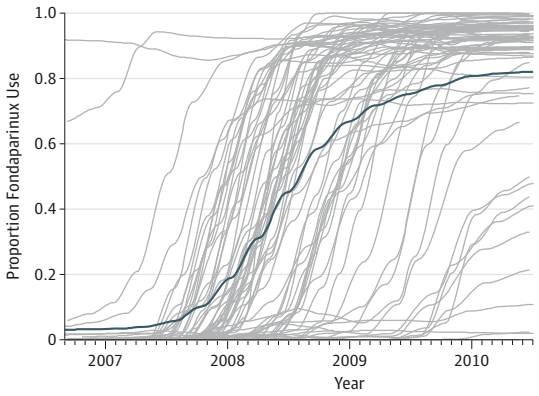
When the combined end-point of MI, stroke, and death events was examined, the OR at 30 days was 0.87 (95% CI, 0.79-0.95) and at 180 days was 0.85 (95% CI, 0.79-0.92). The adjusted odds were lower in the fondaparinux group, and the adjusted odds of death were statistically significant at 30 days (OR, 0.82; 95% CI, 0.71-0.95) and at 180 days (OR, 0.76; 95% CI, 0.68-0.85; Table 2).

## Renal Dysfunction

Fewer patients in the fondaparinux group had at least moderate renal dysfunction (eGFR <60 mL/min/1.73 $m^2$) than did patients in the LMWH group (29.4% vs 35.4%; Table 1). Patients with poorer renal function were older, were more often women, and had more comorbidities (eTable 4 in the Supplement).

Reduced renal function was associated with a more than 5-fold higher bleeding rate in patients with the worst vs normal renal function (eTable 5 in the Supplement). The association between treatment and severe in-hospital bleeding events was similar regardless of renal function (*P* for linear trend > .05), although the CI was wider with lower renal function due to fewer patients (**Figure 2**, eTable 5 in the Supplement). Within each renal function strata, patients in the fondaparinux group

Figure 1. Fondaparinux Use Between 2006 and 2010 in Sweden




Proportion of patients per hospital treated with fondaparinux instead of low-molecular-weight heparin (LMWH) between September 2006 and June 2010 (74 units with ≥100 patients treated are presented of the 86 participating units). The bold line represents all patients treated and entered in the registry.

Table 2. Association Between Use of Fondaparinux and Low-Molecular-Weight Heparin With Various Outcomes

| Events | No. Events/No. All (%) | | OR (95% CI) | | | |
|---|---|---|---|---|---|---|
| | | | | Adjusted | | |
| | Fondaparinux | Low-Molecular-Weight Heparin | Unadjusted | Model 1: Hospital and Calendar Time | Model 2: Hospital, Calendar Time, Baseline Characteristics[a] | Model 3: Model 2+PCI or CABG |
| **In-Hospital** | | | | | | |
| Bleeding | 165/14 791 (1.1) | 461/25 825 (1.8) | 0.62 (0.52-0.74) | 0.47 (0.36-0.60) | 0.54 (0.42-0.70) | 0.54 (0.42-0.70) |
| Death | 394/14 791 (2.7) | 1022/25 825 (4.0) | 0.66 (0.59-0.75) | 0.59 (0.49-0.70) | 0.75 (0.63-0.89) | 0.76 (0.63-0.89) |
| Bleeding or death | 549/14 791 (3.7) | 1429/25 825 (5.5) | 0.65 (0.58-0.72) | 0.54 (0.47-0.63) | 0.67 (0.58-0.78) | 0.68 (0.58-0.79) |
| **30 Days** | | | | | | |
| MI | 1326/14 791 (9.0) | 2463/25 825 (9.5) | 0.93 (0.87-1.00) | 0.93 (0.83-1.04) | 0.94 (0.84-1.06) | 0.95 (0.85-1.06) |
| Stroke | 75/14 791 (0.5) | 153/25 825 (0.6) | 0.86 (0.65-1.13) | 1.02 (0.68-1.13) | 1.11 (0.74-1.65) | 1.12 (0.75-1.68) |
| Death | 628/14 791 (4.2) | 1508/25 825 (5.8) | 0.72 (0.65-0.79) | 0.65 (0.57-0.75) | 0.82 (0.71-0.95) | 0.83 (0.72-0.96) |
| MI, stroke, or death | 1921/14 791 (13.0) | 3932/25 825 (15.2) | 0.83 (0.78-0.88) | 0.79 (0.72-0.86) | 0.87 (0.79-0.95) | 0.88 (0.80-0.96) |
| Bleeding | 204/14 791 (1.4) | 547/25 825 (2.1) | 0.65 (0.55-0.76) | 0.49 (0.39-0.62) | 0.56 (0.44-0.70) | 0.56 (0.44-0.70) |
| Bleeding or death | 807/14 791 (5.5) | 1987/25 825 (7.7) | 0.69 (0.64-0.75) | 0.60 (0.53-0.68) | 0.74 (0.65-0.84) | 0.74 (0.65-0.84) |
| MI, stroke, death, or bleeding | 2077/14 791 (14.0) | 4331/25 825 (16.85) | 0.81 (0.77-0.86) | 0.75 (0.68-0.82) | 0.83 (0.75-0.90) | 0.83 (0.76-0.91) |
| **180 Days** | | | | | | |
| MI | 2100/14 791 (14.2) | 4077/25 825 (15.8) | 0.88 (0.83-0.93) | 0.92 (0.84-1.01) | 0.97 (0.89-1.06) | 0.98 (0.89-1.07) |
| Stroke | 258/14 791 (1.7) | 511/25 825 (2.0) | 0.88 (0.76-1.02) | 0.90 (0.72-1.12) | 0.98 (0.79-1.22) | 0.99 (0.80-1.23) |
| Death | 1234/14 791 (8.3) | 3041/25 825 (11.8) | 0.68 (0.64-0.73) | 0.63 (0.56-0.70) | 0.76 (0.68-0.85) | 0.77 (0.69-0.86) |
| MI, stroke, or death | 3188/14 791 (21.6) | 6704/25 825 (26.0) | 0.78 (0.75-0.82) | 0.76 (0.70-0.82) | 0.85 (0.79-0.92) | 0.86 (0.79-0.93) |
| Bleeding | 285/14 791 (1.9) | 712/25 825 (2.8) | 0.69 (0.60-0.80) | 0.54 (0.44-0.66) | 0.60 (0.50-0.74) | 0.60 (0.50-0.74) |
| Bleeding or death | 1458/14 791 (9.9) | 3598/25 825 (13.9) | 0.68 (0.63-0.72) | 0.60 (0.54-0.72) | 0.71 (0.65-0.72) | 0.72 (0.65-0.80) |
| MI, stroke, death, or bleeding | 3352/14 791 (22.7) | 7103/25 825 (27.5) | 0.77 (0.74-0.81) | 0.73 (0.67-0.78) | 0.81 (0.75-0.88) | 0.82 (0.76-0.89) |

Abbreviation: MI, myocardial infarction.

[a] Baseline characteristics: age; sex; diabetes; hypertension; current smoking status; previous myocardial infarction, congestive heart failure, peripheral vascular disease, ischemic stroke, bleeding, chronic obstructive pulmonary disease, or cancer; Killip classification greater than 1; and estimated glomerular filtration rate. Model 2 is the main model presented in the Results section.

had lower severe in-hospital bleeding rates and a lower adjusted point estimate for severe in-hospital bleeding event than did patients in the LMWH group. This pattern was similar at 30 and 180 days.

Mortality among those with the lowest eGFR was about 20 times higher than those with normal eGFR in both treatment groups (**Figure 3**, eTable 5 in the Supplement). Similar to the main results, there were lower rates and lower adjusted point estimates for in-hospital death for fondaparinux vs LMWH in all renal function categories, except for the small group of patients with eGFR ≤15 mL/min/1.73 m$^2$ (OR, 1.21; 95% CI, 0.55-2.64; Figure 3, eTable 5 in the Supplement). However, *P* for linear trend was not significant (>.05) and the CI was wide in these patients with advanced renal failure due to the low number of patients. This pattern was seen also at 30 and 180 days of follow-up (**Figure 4** and eTable 5 in the Supplement).

## Percutaneous Coronary Intervention

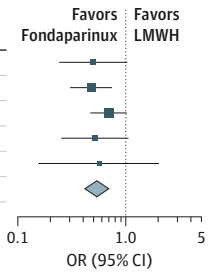
Patients in the fondaparinux group underwent in-hospital PCI more often than did patients in the LMWH group (46.4% vs 38.9%), which is explained by an increased use of PCI with time. Percutaneous coronary intervention–specific adjunctive therapy differed between the 2 treatment groups with unfractionated heparin use (77.6 vs 62.7%) and radial access use (46.3% vs 36.2%) being higher, and lower glycoprotein IIb/IIIa use (12.1% vs 23.5%) in the fondaparinux group (Table 1).

The association between treatment and outcome was not significantly different between patients with and without PCI during hospitalization (*P* for interaction, .27). Among patients undergoing PCI and treated with fondaparinux compared with LMWH, the odds of an in-hospital bleeding event were lower but not statistically significant (OR, 0.89; 95% CI, 0.57-1.38; eTable 6, eFigure 2 in the Supplement). Similarly, the

Figure 2. In-Hospital and 30-Day Bleeding Events by Estimated Glomerular Filtration Rate Strata by Treatment Group

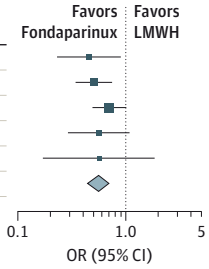
In-hospital bleeding

| Estimated Glomerular Filtration Rate, mL/min/1.73 m$^2$ | Fondaparinux | | LMWH | | OR (95% CI) |
|---|---|---|---|---|---|
| | No. of Events | No. of Patients | No. of Events | No. of Patients | |
| >90 | 20 | 3379 | 52 | 5242 | 0.50 (0.24-1.04) |
| >60-90 | 46 | 7057 | 162 | 11430 | 0.48 (0.31-0.75) |
| >30-60 | 80 | 3718 | 168 | 7204 | 0.70 (0.47-1.03) |
| >15-30 | 14 | 522 | 54 | 1487 | 0.52 (0.25-1.06) |
| ≤15 | 5 | 115 | 25 | 462 | 0.57 (0.16-2.05) |
| All patients | 165 | 14791 | 461 | 25825 | 0.54 (0.42-0.70) |




30-Day bleeding

| Estimated Glomerular Filtration Rate, mL/min/1.73 m$^2$ | Fondaparinux | | LMWH | | OR (95% CI) |
|---|---|---|---|---|---|
| | No. of Events | No. of Patients | No. of Events | No. of Patients | |
| >90 | 22 | 3379 | 60 | 5242 | 0.46 (0.23-0.90) |
| >60-90 | 66 | 7057 | 197 | 11430 | 0.51 (0.35-0.75) |
| >30-60 | 93 | 3718 | 202 | 7204 | 0.71 (0.49-1.01) |
| >15-30 | 17 | 522 | 62 | 1487 | 0.57 (0.29-1.09) |
| ≤15 | 6 | 115 | 26 | 462 | 0.57 (0.17-1.87) |
| All patients | 204 | 14791 | 547 | 25825 | 0.56 (0.44-0.70) |

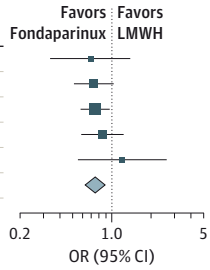



Adjustments were made as in model 2 (hospital, calendar time, and baseline characteristics). LMWH indicates low-molecular-weight heparin.

Figure 3. In-Hospital and 30-Day Mortality by Estimated Glomerular Filtration Rate Strata by Treatment Group

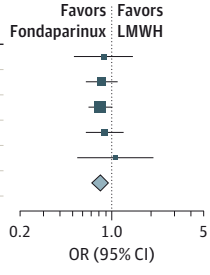
In-hospital mortality

| Estimated Glomerular Filtration Rate, mL/min/1.73 m$^2$ | Fondaparinux | | LMWH | | OR (95% CI) |
|---|---|---|---|---|---|
| | No. of Events | No. of Patients | No. of Events | No. of Patients | |
| >90 | 21 | 3379 | 38 | 5242 | 0.69 (0.34-1.39) |
| >60-90 | 99 | 7057 | 240 | 11430 | 0.73 (0.52-1.03) |
| >30-60 | 183 | 3718 | 459 | 7204 | 0.75 (0.58-0.97) |
| >15-30 | 75 | 522 | 218 | 1487 | 0.85 (0.58-1.24) |
| ≤15 | 16 | 115 | 67 | 462 | 1.21 (0.55-2.64) |
| All patients | 394 | 14791 | 1022 | 25825 | 0.75 (0.63-0.89) |




30-Day mortality

| Estimated Glomerular Filtration Rate, mL/min/1.73 m$^2$ | Fondaparinux | | LMWH | | OR (95% CI) |
|---|---|---|---|---|---|
| | No. of Events | No. of Patients | No. of Events | No. of Patients | |
| >90 | 45 | 3379 | 71 | 5242 | 0.87 (0.52-1.46) |
| >60-90 | 170 | 7057 | 375 | 11430 | 0.85 (0.64-1.12) |
| >30-60 | 282 | 3718 | 659 | 7204 | 0.83 (0.67-1.02) |
| >15-30 | 108 | 522 | 300 | 1487 | 0.89 (0.64- 1.24) |
| ≤15 | 23 | 115 | 103 | 462 | 1.07 (0.55- 2.09) |
| All patients | 628 | 14791 | 1508 | 25825 | 0.82 (0.71- 0.95) |




Adjustments were made as in model 2 (hospital, calendar time, and baseline characteristics). LMWH indicates low-molecular-weight heparin.

point estimate for in-hospital mortality was lower but not statistically significant in the fondaparinux treated group (adjusted OR, 0.67; 95% CI, 0.33-1.05). A similar pattern was found at 30 days for the adjusted odds of bleeding (OR, 0.79; 95% CI, 0.52-1.19) and mortality (OR, 0.85; 95% CI, 0.58-1.25).

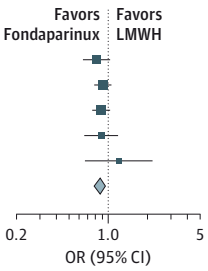
## Sensitivity Analyses

The results in the 3 sensitivity analyses (in patients experiencing an MI for the first time, in complete case analyses, and in matched propensity score analyses) were comparable with the main analyses (eTable 2 in the Supplement).

Figure 4. Thirty-Day Myocardial Infarction, Bleeding, Stroke, or Death by Estimated Glomerular Filtration Rate Strata by Treatment Group

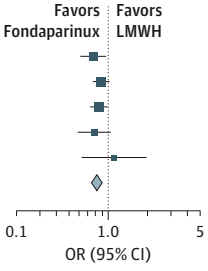
30-Day myocardial infarction, stroke, or death

| Estimated Glomerular Filtration Rate, mL/min/1.73 m$^2$ | Fondaparinux No. of Events | Fondaparinux No. of Patients | LMWH No. of Events | LMWH No. of Patients | OR (95% CI) |
|---|---|---|---|---|---|
| >90 | 299 | 3379 | 509 | 5242 | 0.82 (0.65-1.04) |
| >60-90 | 782 | 7057 | 1455 | 11430 | 0.92 (0.79-1.07) |
| >30-60 | 654 | 3718 | 1380 | 7204 | 0.89 (0.76-1.04) |
| >15-30 | 153 | 522 | 435 | 1487 | 0.89 (0.66-1.20) |
| ≤15 | 33 | 115 | 153 | 462 | 1.21 (0.67-2.19) |
| All patients | 1921 | 14791 | 3932 | 25825 | 0.87 (0.79- 0.95) |




30-Day myocardial infarction, stroke, bleeding, or death

| Estimated Glomerular Filtration Rate, mL/min/1.73 m$^2$ | Fondaparinux No. of Events | Fondaparinux No. of Patients | LMWH No. of Events | LMWH No. of Patients | OR (95% CI) |
|---|---|---|---|---|---|
| >90 | 318 | 3379 | 560 | 5242 | 0.78 (0.62-0.97) |
| >60-90 | 834 | 7057 | 1593 | 11430 | 0.89 (0.77-1.03) |
| >30-60 | 726 | 3718 | 1527 | 7204 | 0.85 (0.73-1.00) |
| >15-30 | 162 | 522 | 479 | 1487 | 0.79 (0.59-1.06) |
| ≤15 | 37 | 115 | 172 | 462 | 1.11 (0.63-1.97) |
| All patients | 2077 | 14791 | 4331 | 25825 | 0.83 (0.75-0.90) |




Adjustments were made as in model 2 (hospital, calendar time, and baseline characteristics). LMWH indicates low-molecular-weight heparin.

## Discussion

This study compares the anticoagulant fondaparinux with LMWH in a nationwide complete register of patients with NSTEMI treated in routine clinical care. Our main finding is that the use of fondaparinux, compared with LMWH, was associated with a lower risk of bleeding events and death both in short-term and long-term follow-up, but similar rates of MI and stroke. The results were similar in patients with varying degrees of renal function. Finally, the results were also similar in the subgroup of patients with NSTEMI who had undergone early PCI.

A randomized clinical trial is often needed to provide definite evidence and an estimate of the treatment effect in a specific, selected, well-defined target patient population. However, the effect of implementing the same treatment in clinical practice might differ and should therefore be investigated in observational cohorts and, preferably, in continuous registries with complete coverage of nonselected patients with an indication for the studied treatment. Outside of a trial setting, the treatment is given to a much more heterogeneous patient population and the treating centers and physicians are less selected. Thus, the balance between benefit and risk can differ between a randomized clinical trial and experience in a nontrial, routine clinical care setting.[14,15] Therefore, experiences from clinical practice provide important complementary information.

In this study of nearly all patients with NSTEMI treated with fondaparinux or LMWH in Sweden between 2006 and 2010, the median age was 73 years, which is about 5 years older than the median age in the OASIS-5 trial. Patients in this trial compared with those in the OASIS-5 trial had similar rates of diabetes (26.4% vs 25.0%), a lower rate of hypertension (55.7% vs 67.1%), and more frequent history of MI (30.7% vs 25.7%) and stroke (11.3% vs 6.5%). More patients in this study had at least a moderate renal dysfunction (33.2% vs 12.9%) than patients in the OASIS-5 trial. The results from our study provide more certainty to the use of fondaparinux in routine clinical care, showing that in the broader population, the lower bleeding and death rates associated with fondaparinux treatment were consistent with the trial data.

The lower mortality with fondaparinux compared with LMWH in the OASIS-5 trial was attributed to the lower bleeding rates, possibly related to fondaparinux's different mechanism of action (factor Xa vs factor Xa and IIa inhibition), a more adjusted and relatively lower anticoagulant effect at the given dose, or both.[16] Bleeding events are associated with a higher risk of adverse outcomes.[1,17,18]

The results with lower odds of bleeding with fondaparinux compared with LMWH treatment among patients with reduced renal function were consistent with the entire study population. Similar results were observed in the renal OASIS-5 substudy.[4] Patients with renal dysfunction are at high risk of bleeding events, and if bleeding events can be prevented this may translate into lower mortality. However, even though the odds of bleeding were consistently lower across all renal function categories, the lower mortality with fondaparinux compared with LMWH was not significant in those with worst renal function. This may indicate that the elevated risk of death in those with the lowest renal function category is explained by other mechanisms unrelated to bleeding.

Current European Society of Cardiology (ESC)[19] and American Heart Association–American College of Cardiology (AHA/ACC) guidelines[20] recommend anticoagulant use for the treatment of patients with NSTEMI, but their recommendations differ. Whereas ESC guidelines propose fondaparinux as a first-choice anticoagulant for both patients treated either noninvasively or with PCI, ACC/AHA guidelines recommend either fondaparinux or enoxaparin to patients who do not undergo PCI and do not provide specific anticoagulant recommendation for patients who do. In this study, we found that in a nonselected NSTEMI population among whom 41.6% were treated with PCI, fondaparinux was overall associated with favorable outcomes compared with LMWH. We also observed lower odds of bleeding and death (although not statistically significant) among PCI-treated patients receiving fondaparinux, which is consistent with the post hoc study from the OASIS-5 trial.[5]

This study has limitations that need to be considered for the correct interpretation of our findings. This is not a randomized trial; therefore, residual confounding is very likely. Conclusions regarding the degree of treatment effect should be done with caution. Although there was a consistent pattern of lower adjusted odds of bleeding throughout the study with the use of fondaparinux compared with LMWH, the number of bleeding events is likely an underestimate. Bleeding events are often underreported in real-life health care and in a registry. Furthermore, the dose and duration of fondaparinux and LMWH were not recorded. However, the study reflects the situation when results from trials and practice guidelines are translated into clinical reality.

## Conclusions

In routine clinical care of patients with NSTEMI, fondaparinux compared with LMWH was associated with lower odds of major bleeding events and death both in-hospital and up to 180 days.

### ARTICLE INFORMATION

**Author Affiliations:** Section of Cardiology, Department of Medicine, Huddinge, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden (Szummer, Edfors, Jernberg); Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, Uppsala, Sweden (Oldgren, Wallentin); Uppsala Clinical Research Center, Uppsala, Sweden (Lindhagen); Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden (Carrero, Evans); Division of Cardiovascular Medicine, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden (Spaak); Division of Nephrology, Department of Clinical Sciences, Karolinska Institutet, Danderyd Hospital, Stockholm, Sweden (Jacobson); Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden (Andell).

**Author Contributions:** Dr Jernberg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Szummer, Oldgren, Carrero, Evans, Edfors, Andell, Jernberg.
*Acquisition, analysis, or interpretation of data:* Oldgren, Lindhagen, Carrero, Evans, Spaak, Jacobson, Andell, Wallentin, Jernberg.
*Drafting of the manuscript:* Szummer, Lindhagen, Carrero, Edfors.
*Critical revision of the manuscript for important intellectual content:* Szummer, Oldgren, Lindhagen, Carrero, Evans, Spaak, Jacobson, Andell, Wallentin, Jernberg.
*Statistical analysis:* Lindhagen.
*Obtained funding:* Jernberg.
*Administrative, technical, or material support:* Jacobson, Jernberg.
*Study supervision:* Wallentin, Jernberg.

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Jernberg reports consulting for and receiving lecture fees from AstraZeneca. Dr Szummer reports receiving lecture fees from AstraZeneca. Dr Oldgren reports receiving consulting and lecture fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. Dr Evans reports receiving payment for lectures for Amgen. Dr Spaak reports receiving grant funding from AbbVie; payment for lectures from Abbot and Merck; payment for the development of educational presentations from MSD; travel accommodations from Medtronic; and receiving support from the Karolinska Cardiorenal Theme Center. Dr Jacobson reports receiving support from the Karolinska Cardiorenal Theme Center and payment for lectures from Amgen and Fresenius Medical Care. Dr Wallentin reports receiving research grants from AstraZeneca, Merck & Co, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, and GlaxoSmithKline; serving as a consultant for Abbott, Merck & Co, Regado Biosciences, Athera Biotechnologies, Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; lecture fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline; honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline; and travel support from AstraZeneca, Bristol-Myers Squibb/Pfizer, and GlaxoSmithKline. No other disclosures were reported.

**Funding/Support:** This work was supported by a grant from the Swedish Foundation for Strategic Research, the Swedish Heart and Lung Foundation, ALF Medicin (the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Institutet; Drs Szummer, Evans, Carrero), the Swedish Medical Research Council (Dr Carrero).

**Role of the Funder/Sponsor:** The funder was not involved in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

**Correction:** This article was corrected on February 19, 2015, to fix a typographical error in a subtitle.

### REFERENCES

1. Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114(8):774-782.

2. Yusuf S, Mehta SR, Chrolavicius S, et al; 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(14):1464-1476.

3. Santopinto JJ, Fox KA, Goldberg RJ, et al; 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(9):1003-1008.

4. Fox KA, Bassand JP, Mehta SR, et al; OASIS 5 Investigators. Influence of renal function on the efficacy and safety of fondaparinux relative to enoxaparin in non-ST-segment elevation acute coronary syndromes. *Ann Intern Med*. 2007;147(5):304-310.

5. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol*. 2007;50(18):1742-1751.

6. Bassand JP, Hamm CW, Ardissino D, et al; Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology. Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J*. 2007;28(13):1598-1660.

7. Jernberg T, Attebring MF, Hambraeus K, et al. The Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). *Heart*. 2010;96(20):1617-1621.

8. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.

9. Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration

rate with standardized serum creatinine values. *Clin Chem*. 2007;53(4):766-772.

**10**. Skali H, Uno H, Levey AS, Inker LA, Pfeffer MA, Solomon SD. Prognostic assessment of estimated glomerular filtration rate by the new Chronic Kidney Disease Epidemiology Collaboration equation in comparison with the Modification of Diet in Renal Disease Study equation. *Am Heart J*. 2011;162(3):548-554.

**11**. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3(1):1-50.

**12**. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med*. 2011;30(4):377-399.

**13**. Fraser SGaM. *Propensity Score Analysis: Statistical Methods and Applications. Advanced Quantitative Techniques in the Social Scienses*. Thousand Oaks: SAGE Publications; 2009.

**14**. Friberg L. Safety of dronedarone in routine clinical care. *J Am Coll Cardiol*. 2014;63(22):2376-2384.

**15**. Hohnloser SH. Dronedarone: "real-world" data vis-à-vis data from randomized clinical trials. *J Am Coll Cardiol*. 2014;63(22):2385-2387.

**16**. Anderson JA, Hirsh J, Yusuf S, et al. Comparison of the anticoagulant intensities of fondaparinux and enoxaparin in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-5 trial. *J Thromb Haemost*. 2010;8(2):243-249.

**17**. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. *Am J Cardiol*. 2005;96(9):1200-1206.

**18**. Mehran R, Pocock SJ, Nikolsky E, et al. A risk score to predict bleeding in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2010;55(23):2556-2566.

**19**. Hamm CW, Bassand JP, Agewall S, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2011;32(23):2999-3054.

**20**. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(23):e179-e347.