

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: The 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.

Web Appendix 1: OASIS-5 DEFINITIONS OF STUDY OUTCOMES

Death

Deaths are classified as cardiovascular or non-cardiovascular. All deaths with a clear cardiovascular or unknown cause are classified as cardiovascular. However, within cardiovascular deaths, hemorrhagic deaths are clearly identified. Only deaths due to a documented non-cardiovascular cause (e.g., cancer) will be classified as non-cardiovascular.

Acute myocardial infarction

An associated MI is defined as myocardial infarction associated with presenting symptoms initially diagnosed on admission as ACS (UA or MI without ST segment elevation), with subsequent rise in cardiac enzymes/markers or persistent ECG changes such that the diagnosis is myocardial infarction. Although associated MI is not a study outcome, the definition of acute myocardial infarction depends on the presence of an Associated MI.

The definition of Acute Myocardial Infarction is complicated relating to the presence or absence of associated MI, the timing after randomization, and the association with PCI or CABG. The definition of Acute MI is therefore encompasses these various factors as follows:

In patients without an associated baseline MI, the criteria for an acute, evolving or recent MI within 7 days of randomization is either pathological findings of an acute MI or a typical rise and fall of biochemical markers of myocardial necrosis (including troponin, CK-MB, CK) to greater than 2x ULN (or if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction) with at least one of ischemic symptoms, the development of pathological Q waves on the ECG, ECG changes indicative of ischemia (ST-segment elevation or depression), or coronary artery intervention.

In patients with an associated MI at baseline, a new MI within 24 hours of randomization requires new ischemic symptoms greater than 20 minutes as well as new or recurrent ST segment elevation or depression greater than 0.1 millivolt in at least 2 contiguous leads. In patients with an associated MI at baseline, a new MI between 24 hours and 7 days is defined as ischemic symptoms greater than 20 minutes and either CK-MB (or total CK if CK-MB not available) at least 2x the upper limit of normal (or >50% above the previous valley level in patients with already elevated enzymes) or new or recurrent ST segment elevation or depression > 0.1 millivolt or new significant Q-waves in at least 2 contiguous leads discrete from the baseline MI

In all patients, the definition of new MI occurring after 7 days of randomization, the criteria for an acute, evolving or recent MI within 7 days of randomization is

either pathological findings of an acute MI or a typical rise and fall of biochemical markers of myocardial necrosis (including troponin, CK-MB, CK) to greater than 2x ULN (or if markers already elevated, greater than 50% of the lowest recovery enzyme level from the index infarction) with at least one of ischemic symptoms, the development of pathological Q waves on the ECG, ECG changes indicative of ischemia (ST-segment elevation or depression), or coronary artery intervention.

Within 48 hours of PCI, a new MI is defined by CK-MB (or total CK, if CK-MB is unavailable) greater than 3x the upper limit of normal (or increased by 50% from the pre-procedural valley level and >3x ULN in patients with already elevated enzymes) or new ST segment elevation or development of significant Q-waves in at least 2 contiguous leads. Similarly, within 48 hours of CABG surgery, an acute MI is defined by CK-MB (or total CK, if CK-MB is unavailable) at least 5x the upper limit of normal (or increased by 50% from the pre-procedural valley level and greater than 5x ULN in patients with already elevated enzymes) or new significant Q-wave in at least 2 contiguous leads.

In all cases of new MI, troponin T or I may be used for the diagnosis of new MI in the absence of CK-MB at the discretion of the Event Adjudication Committee taking into consideration all available clinical and laboratory evidence of new MI.

Refractory and Severe Ischemia

Ischemia is classified as either refractory or severe. Refractory Ischemia is defined as recurrent chest pain or ischemic symptoms lasting more than 5 minutes while on optimal medical therapy (at least 2 anti-anginal treatments) with documented characteristic ECG changes indicative of ischemia and requiring an additional intervention. An additional intervention is defined as thrombolytic therapy for threatened MI, cardiac catheterization, insertion of intra-aortic balloon pump or revascularization procedure (PCI or CABG surgery) within 48 hours of the onset of this episode.

Severe Ischemia is defined as recurrent chest pain/ischemic symptoms lasting more than 5 minutes while on optimal medical therapy with documented characteristic ECG changes indicative of ischemia which may or may not require an intervention after 48 hours.

Stroke

Stroke is defined as the presence of a new focal neurologic deficit thought to be vascular in origin with signs or symptoms lasting more than 24 hours. Stroke is further classified as ischemic, hemorrhagic or type uncertain.

Major Bleeding

Major bleeding is defined as clinically overt bleeding that is either fatal, a symptomatic intracranial hemorrhage, a retroperitoneal hemorrhage, an intraocular hemorrhage leading to significant vision loss, a decrease in hemoglobin of at least 3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL of Hb), or bleeds requiring transfusion of two or more units of red blood cells or equivalent of whole blood.

Minor Bleeding

Minor bleeding is considered to be any other clinically significant bleeding not meeting the definition for major bleeding and leading to interruption of study drug for at least 24 hours, surgical intervention or transfusion of one unit of blood (whole blood or PRBC).

Bleeding according to TIMI criteria

In order to provide the same assessment of bleeding as the one performed in the OASIS 6 study (in patients with ST elevation ACS), all reported bleeding will be classified according to the TIMI classification. According to this classification, the following bleeding will be considered as severe: fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a clinically significant hemorrhage with a decrease in hemoglobin (Hb) of at least 5 g/dL, with each blood transfusion unit counting for 1.0 g/dL of Hb. Bleeding will be further classified as to whether it was CABG related (i.e., within 7 days of CABG surgery) or non-CABG related.

Web Appendix 2: PCI: Study Drug Administration

Study Drug Administration and Concomitant treatment

Study Drug should be started immediately after randomization. Patients will be randomized to fondaparinux 2.5 mg subcutaneous injection once daily or weight adjusted enoxaparin (1 mg/kg) b.i.d. subcutaneous injections (or 1 mg/kg once daily if creatinine clearance is between 20 mL/min and 30 mL/min). Visually matching syringes will be used for fondaparinux, enoxaparin and placebo.

In order to satisfy the double blinding, patients will receive double dummy administration of either fondaparinux and placebo-enoxaparin or enoxaparin and placebo-fondaparinux. In any case study drug administration will start with the simultaneous administration of (enoxaparin and placebo fondaparinux) or (placebo-enoxaparin and fondaparinux).

The fondaparinux or fondaparinux-placebo subcutaneous injection should be administered once daily at 24 hour intervals (\pm 4 hours) and the enoxaparin or enoxaparin-placebo should be administered twice daily at 12 hour intervals (\pm 2 hours). In case of PCI, where enoxaparin or enoxaparin-placebo is replaced by UFH or UFH-placebo, please see table below).

Study drug administration during PCI

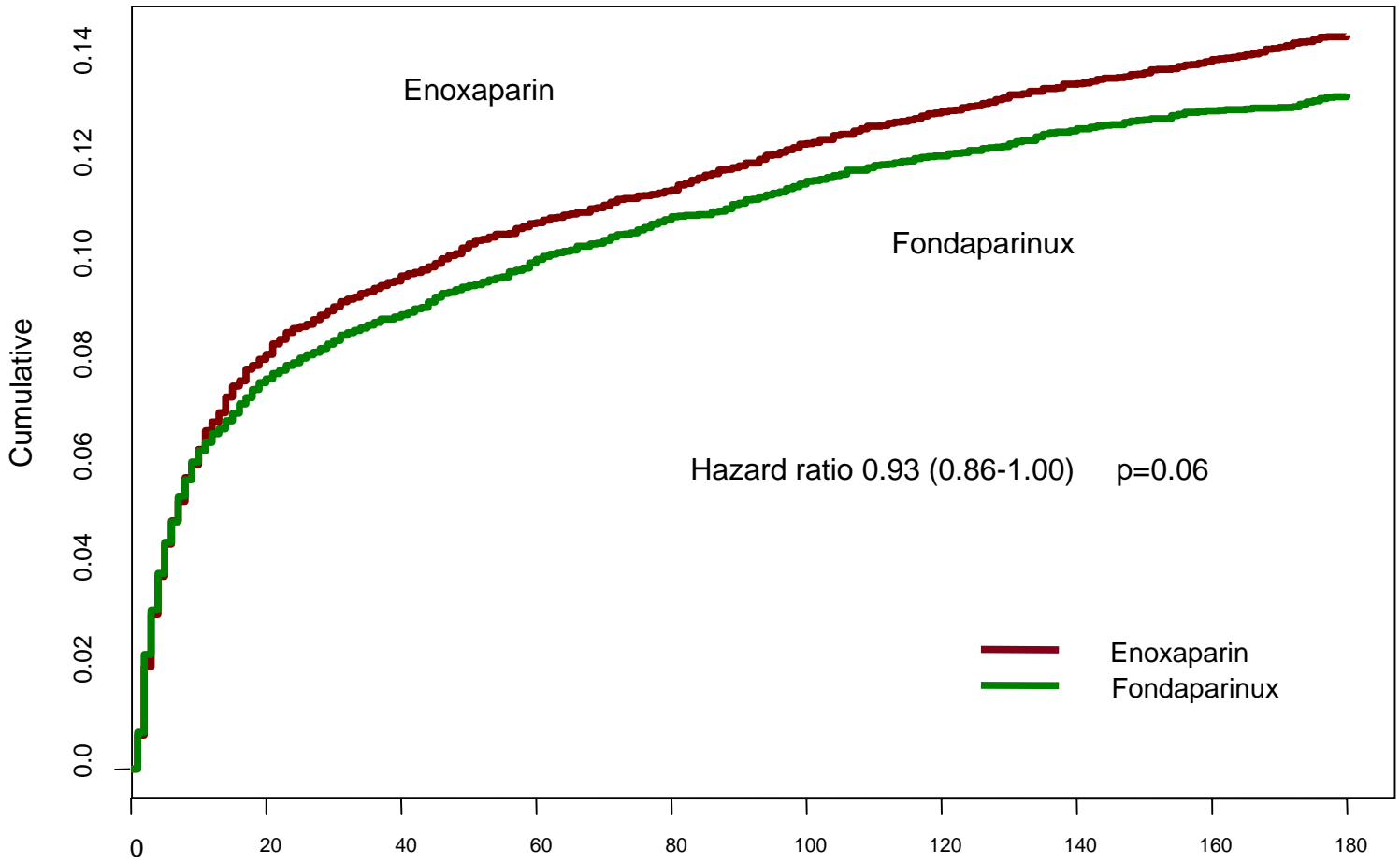
	TIME SINCE LAST INJECTION(S)		
	≤ 6 hours		> 6 hours
	Last injection Double (fonda/placebo +enox/placebo)	Last injection Single (enox/placebo ONLY)	Last injection Double or single
With GP IIb/IIIa	NO STUDY DRUG	Fonda/placebo 2.5 mg IV	Fonda/placebo 2.5 mg IV + UFH/placebo 0.013 mL/kg IV (65u/kg)
Without GP IIb/IIIa	Fonda/placebo 2.5 mg IV	Fonda/placebo 5.0 mg IV	Fonda/placebo 5.0 mg IV + UFH/placebo 0.02 mL/kg IV (100u/kg)

Permitted or recommended concomitant therapy

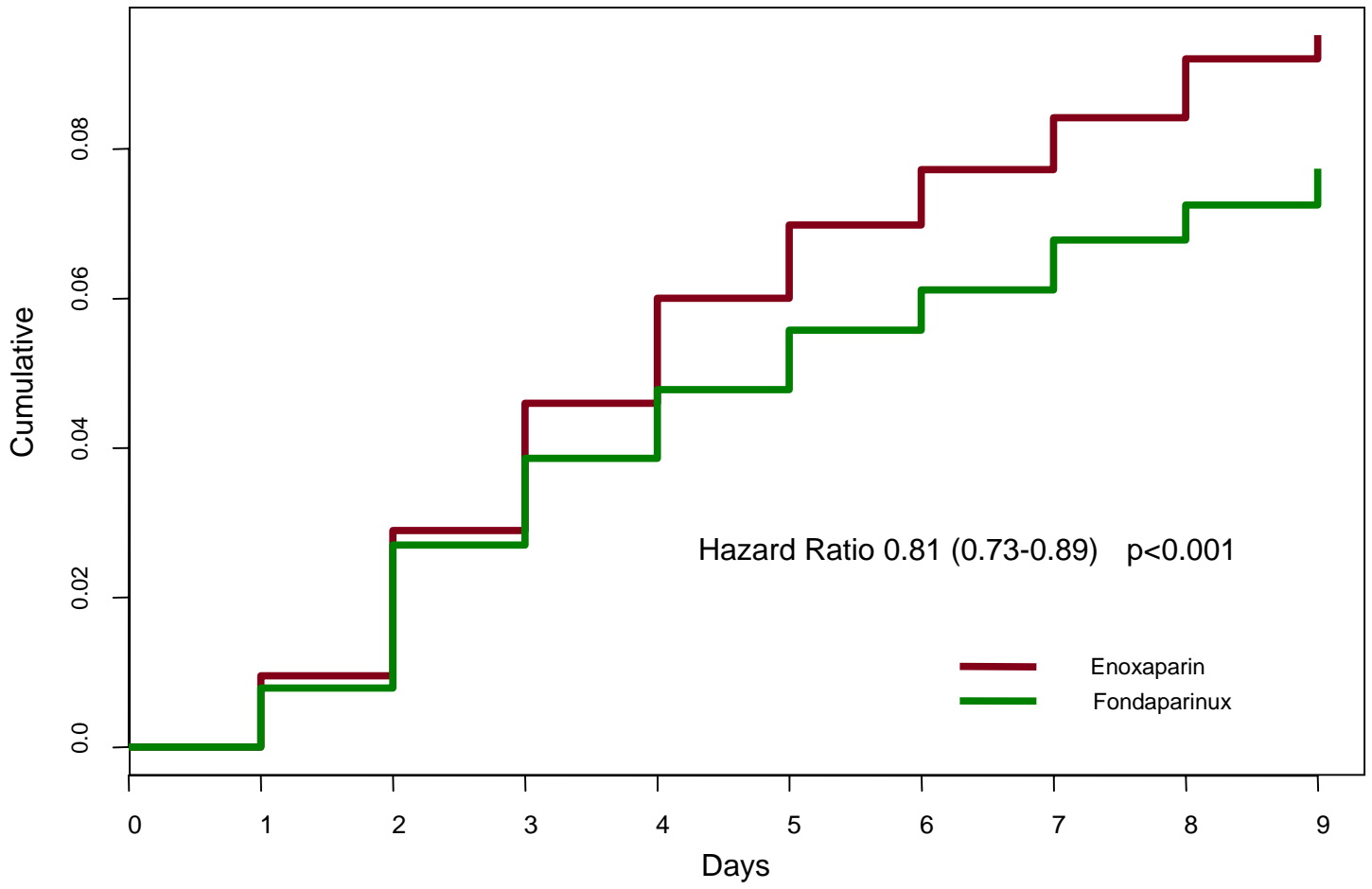
All patients should receive all other standard medical treatments for UA/NSTEMI, including ASA (100 to 325 mg once daily), and other antithrombotic therapy (e.g., clopidogrel, ticlopidine GPIIb/IIIa receptor antagonists etc.) at the investigator's discretion.

Arterial and/or venous line flushes: saline flushes are strongly recommended but heparin flushes are permitted up to 200 IU/day.

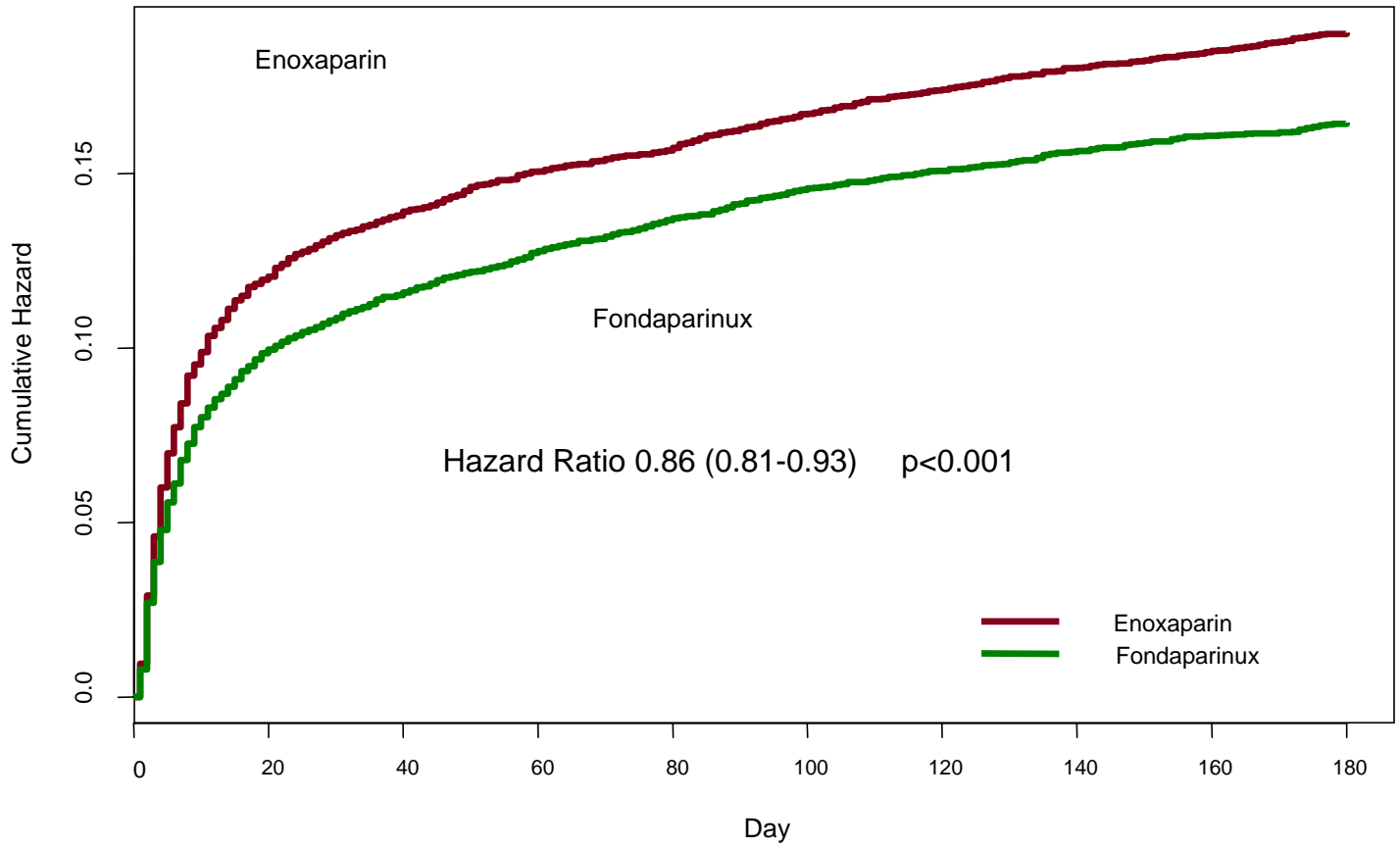
Web Figure 1: Death, MI, Refractory Ischemia up to Day 180



Web Figure 2: Death, MI, Refractory Ischemia, Major Bleeding up to Day 9



Web Figure 3: Death, MI, Refractory Ischemia, Major Bleeding Up to Day 180



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