RESEARCH

Efficacy and safety of unfractionated heparin versus enoxaparin: a pooled analysis of ASSENT-3 and -3 PLUS data

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ABSTRACT

Background: The optimal antithrombotic therapy to accompany tenecteplase in cases of acute ST-segment elevation myocardial infarction (STEMI) remains unclear. We undertook a prespecified pooled analysis of data from the ASSENT-3 and ASSENT-3 PLUS trials.

Methods: We created a combined database of the 2040 and 818 patients who received enoxaparin in ASSENT-3 and ASSENT-3 PLUS, respectively, and compared them with the 2038 and 821 patients who received unfractionated heparin.

Results: The primary efficacy end point, a composite of 30-day mortality, reinfarction or refractory ischemia, was 16.0% with enoxaparin versus 12.2% with unfractionated heparin ($p < 0.001$); the efficacy plus safety (intracranial hemorrhage [ICH] or major systemic bleeding) end point, 18.0% versus 15.0% ($p = 0.003$). The 1049 patients urgently revascularized had greater benefit from enoxaparin (15.4% v. 10.1%, $p = 0.013$), yet the excess in major systemic bleeding evident with enoxaparin (3.3% v. 2.4%, $p = 0.01$) was largely confined to the 3492 patients without or before revascularization. Although ICH rates in the groups were similar (1.3% v. 0.9%, $p = 0.26$), an excess of ICH occurred among those administered enoxaparin during the ASSENT-3 PLUS trial (6.7% v. 0.8%, $p = 0.013$), especially among women over 75 years of age.

Interpretation: These data demonstrated the benefit of enoxaparin used in conjunction with tenecteplase, but raised caution about its prehospital use to treat STEMI in elderly women.

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The best antithrombotic therapy to accompany fibrinolysis for acute ST-segment elevation myocardial infarction (STEMI) remains uncertain. In ASSENT-3, the Assessment of the Safety and Efficacy of a New Thrombolytic Agent trial, we showed that the combination of enoxaparin and tenecteplase was more effective than unfractionated heparin plus tenecteplase in reducing ischemic complications in patients treated within 6 hours of onset of symptoms of STEMI.[1] Although patients treated with enoxaparin experienced a modest excess in the incidence of major systemic

bleeding, the enoxaparin–tenecteplase combination was administered continuously until either hospital discharge or revascularization (maximum 7 days), whereas unfractionated heparin plus tenecteplase was terminated after 48 hours. Because the incidence of intracranial hemorrhage (0.9%) was the same with either treatment strategy and was commensurate with rates found in other studies of fibrinolytic agents, we asserted that enoxaparin was an attractive alternative antithrombotic and deserved further study.

In a planned extension of ASSENT-3 involving patients with the same clinical characteristics in the prehospital setting (ASSENT-3 PLUS), tenecteplase administration was accompanied by either unfractionated heparin or enoxaparin. We confirmed that the enoxaparin combination reduced reinfarction and recurrent ischemia more than the unfractionated heparin combination, with an excess in major systemic bleeding in keeping with that seen in ASSENT-3. We also observed an unexpected increase in intracranial hemorrhage among the patients in the enoxaparin group who were older than 75 years.[2]

We now report on a pooled analysis (with a prespecified strategy) of data from ASSENT-3 and ASSENT-3 PLUS to provide an overall efficacy and safety profile of these 2 antithrombotic strategies (i.e., enoxaparin and unfractionated heparin) used in conjunction with tenecteplase to treat STEMI.

Methods

Our findings from ASSENT-3 and ASSENT-3 PLUS have been previously reported.[1,2] In brief, patients with STEMI were randomly assigned in ASSENT-3 to receive a single intravenous (IV) bolus of tenecteplase in combination with enoxaparin, abciximab plus low-dose unfractionated heparin, or a typical dose of unfractionated heparin. In ASSENT-3 PLUS, patients with STEMI were randomly assigned to receive a single IV bolus of tenecteplase with either enoxaparin or unfractionated heparin in the prehospital setting. For the current pooled analysis, we included ASSENT-3 data only from the groups receiving enoxaparin ($n = 2040$) or unfractionated heparin ($n = 2038$). ASA (150–325 mg) was given to all patients, who continued taking it daily at a similar dose. A weight-adjusted dose of tenecteplase (30 mg if the patient weighed < 60 kg, 35 mg if 60–69 kg, 40 mg if 70–79 kg, 45 mg if 80–89 kg and 50 mg if ≥ 90 kg) was administered over a 5-second period. Patients assigned to

the unfractionated heparin group received a 60-unit/kg bolus (maximum 4000 units) and an initial infusion of 12 units/kg per hour (maximum 1000 units/h), which was adjusted to maintain an activated partial thromboplastin time (aPTT) of 50–70 seconds for 48 hours. Those assigned to the enoxaparin group received an IV bolus of 30 mg followed by a subcutaneous dose of 1 mg/kg; the subcutaneous dose was repeated every 12 hours until hospital discharge or revascularization (maximum 7 days); the first 2 subcutaneous doses had an upper limit of 100 mg. Patients involved in the ASSENT-3 PLUS trial were similarly evaluated, randomly assigned and treated in the prehospital setting, in accordance with local resources.

The 2 trials had 2 primary end points, both composites: efficacy (30-day mortality, in-hospital reinfarction or refractory ischemia); and efficacy plus safety (the aforementioned efficacy end points, plus in-hospital intracranial hemorrhage or other major bleeding). An independent Stroke Evaluation Panel unaware of group assignments reviewed all cases of suspected stroke; the investigators ascertained the other end points.[1]

We specified a detailed statistical analysis plan beforehand for a combined intention-to-treat analysis of the ASSENT-3 PLUS treatment groups and the correspondinga two ASSENT-3 groups. This included pooled estimates of both primary efficacy and safety end points and their single components, in addition to between-group comparisons, to be presented as odds ratios (ORs) with confidence limits. We specified and used backward stepwise logistic regression to estimate adjusted ORs and 95% confidence intervals (CIs) for these end points, adjusted not only for treatment-group assignment but also for baseline patient characteristics: age, sex, body height and weight; presence of diabetes or hypertension; heart rate and systolic blood pressure; Killip class; and time interval until treatment.[3] For purposes of performing logistic regression analyses, another category was created for the 21% of ASSENT-3 PLUS participants whose Killip class data were missing. Kaplan–Meier survival analyses with log-rank tests were performed to test the differences between the treatment arms. We also undertook post-hoc subgroup analyses to explore the possible effect of urgent and nonurgent revascularization on the relations between the treatment agents and 2 in-hospital outcomes (reinfarction and major systemic bleeding) by data censoring at the time of revascularization. All statistical tests were 2-sided, with the level of significance set at 5%.

Results

Baseline characteristics (Table 1; note that a more detailed version is available online as Appendix 1 at www.cmaj.ca /cgi /content/full/174/10/1421/DC1) and concomitant medication use (Table 2) are shown for participants in the ASSENT-3 and ASSENT-3 PLUS trials. Patients in ASSENT-3 PLUS were slightly older, with a greater proportion older than 75 years, especially among the women. There were also more patients in ASSENT-3 PLUS with anterior myocardial infarctions (MIs) and a greater use of statins and thienopyridine therapy.

Table 3 shows the frequency of in-hospital events and use of invasive cardiac procedures. The frequency of invasive cardiac procedures, and more particularly of urgent and nonurgent

PCI, were notably higher among ASSENT-3 PLUS participants.

Fig. 1 presents a pooled analysis of the primary efficacy and the composite of primary efficacy plus safety end points; selected individual components of these are shown according to antithrombotic treatment assignment. A consistent reduction in both reinfarction and recurrent ischemia was evident in the enoxaparin group, with no significant effect on the rate of death; this constitutes the principal beneficial effect of this antithrombotic on the primary efficacy end point. Of note, 13 of the 97 patients who died during ASSENT-3 PLUS expired before hospital admission; these deaths were evenly balanced between the treatment groups (i.e., 6 patients who died received enoxaparin and 7, unfractionated heparin). If these deaths are excluded, the mortality was 5.2% in the unfractionated heparin group and 6.8% in the enoxaparin group. The 1% absolute increase in major systemic bleeding and in intracranial hemorrhage evident with enoxaparin in ASSENT-3 PLUS lessen, but do not cancel, its favourable effect on the primary efficacy and safety end point. These findings were maintained after baseline adjustments: OR 1.40 (95% CI 1.19–1.64) for the primary efficacy end point and 1.25 (95% CI

Table 1: Baseline characteristics of patients in the ASSENT-3 PLUS and ASSENT-3 trials

| Characteristic | % of treatment group* | | | |
| | ASSENT-3 PLUS | | ASSENT-3 | |
	Enox. n = 818	UFH n = 821	Enox. n = 2040	UFH n = 2038
Age, yr, mean (SD)	62 (13)	62 (13)	61 (12)	61 (13)
% of patients > 75 yr	18	16	13	13
Women	24	22	23	23
% of women > 75 yr	38	30	24	27
Hypertension	35	36	41	41
Diabetes	14	16	19	18
Previous MI	15	14	14	14
Prior CABG	2.6	1.6	3.6	2.6
Prior PCI	7.4	6.4	6.2	6.4
Current smoker	42	45	44	47
Infarct location				
Anterior	42	43	39	38
Inferior	54	54	56	57
Other	4.0	3.2	4.6	5.0
Heart rate, beats/min, mean (SD)	74 (19)	74 (19)	75 (17)	74 (17)
Systolic BP, mm Hg, mean (SD)	134 (25)	132 (25)	134 (22)	133 (23)
Killip class I†	92	92	89	88

Note: A more detailed version of this table is available online (at www.cmaj.ca /cgi/content/full/174/10/1xxx/DC1) as Appendix 1. ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent, Enox. = enoxaparin, UFH = unfractionated heparin, SD = standard deviation, MI = myocardial infarction, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention, BP = blood pressure.
*Unless indicated otherwise.
†Killip class was unrecorded in the records of 21% of ASSENT-3 PLUS patients.

1.07–1.45) for the primary efficacy plus safety end point. Similar efficacy patterns were evident in subsets of patient data categorized by age, sex and presence of diabetes.

Data showing the beneficial effect of enoxaparin on in-

Table 2: Concomitant medication of patients, no. (%), in the ASSENT-3 PLUS and ASSENT-3 trials.

Medication	No. of patients (%)			
	ASSENT-3 PLUS		ASSENT-3	
	Enoxaparin n ≃ 815*	UF heparin n ≃ 818†	Enoxaparin n ≃ 2034‡	UF heparin n ≃ 2030§
Nitrates, intravenous	495 (61)	507 (62)	1490 (73)	1489 (73)
β-Blocker	734 (90)	725 (89)	1707 (84)	1696 (83)
ACE or other inhibitor	509 (62)	539 (66)	1300 (64)	1303 (64)
Statin	604 (74)	574 (70)	1062 (52)	1024 (51)
ASA	784 (96)	792 (97)	1969 (97)	1974 (97)
Ticlopidine or clopidogrel	444 (55)	455 (56)	605 (30)	649 (32)
Oral anticoagulant	37 (4.5)	34 (4.2)	87 (4.3)	105 (5.2)
GP-IIb/-IIIa inhibitor	147 (18)	170 (21)	262 (13)	312 (15)
LMW heparin¶	268 (33)	389 (47)	325 (16)	584 (29)
Thrombolytic agent¶	20 (2.4)	17 (2.1)	40 (2.0)	58 (2.9)

Note: ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent, UF = unfractionated, ACE = angiotensin-converting enzyme, GP = glycoprotein, LMW = low molecular weight.
*Range of n was 813-817.
†Range of n was 816-820.
‡Range of n was 2027-2040.
§Range of n was 2023-2036.
¶Other than the study drug.

Table 3: In-hospital cardiac events and invasive procedures in the ASSENT-3 PLUS and ASSENT-3 trials

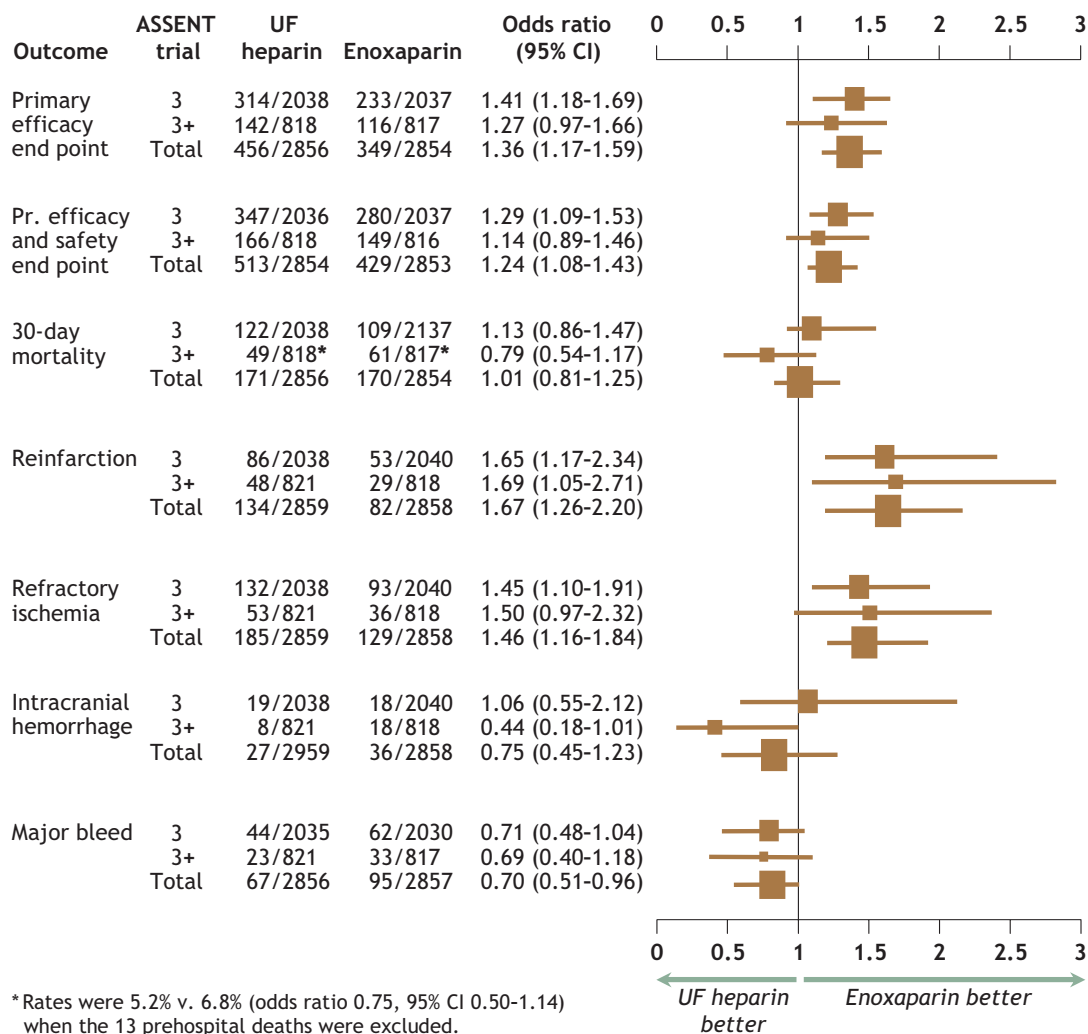| Status	No. (%)			
	ASSENT-3 PLUS		ASSENT-3	
	Enoxaparin	UF heparin	Enoxaparin	UF heparin
Cardiac event	n = 818	n = 821	n = 2040	n = 2038
Sustained hypotension	16 (2.0)	25 (3.0)	42 (2.1)	55 (2.7)
Pulmonary edema or cardiogenic shock	43 (5.3)	52 (6.3)	106 (5.2)	115 (5.6)
Major arrhythmia	71 (8.7)	81 (9.9)	173 (8.5)	212 (10.4)
Stroke	24 (2.9)	11 (1.3)	33 (1.6)	31 (1.5)
Procedure	n ≃ 815*	n = 813	n ≃ 2037*	n ≃ 2035*
Intra-aortic balloon pump	13 (1.6)	19 (2.3)	53 (2.6)	56 (2.8)
CABG, urgent	8 (1.0)	15 (1.8)	34 (1.7)	34 (1.7)
CABG, elective	19 (2.3)	21 (2.6)	48 (2.4)	71 (3.5)
PCI, urgent	204 (25.0)	239 (29.4)	242 (11.9)	292 (14.3)
PCI, elective	190 (23.3)	183 (22.5)	355 (17.4)	335 (16.5)
All procedures	413 (50.7)	446 (54.9)	661 (32.4)	718 (35.3)

Note: ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent, UF = unfractionated, CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention.
*± 1 patient, according to the data available.

hospital reinfarction up until 14 days after group assignment, according to whether patients underwent in-hospital revascularization, is available in online Appendix 2 (www.cmaj.ca/cgi/content/full/174/10/1421/DC1). In this analysis, the no-revascularization cohort was defined for all patients by censoring on the right at the time of revascularization. Rates of reinfarction according to Kaplan–Meier estimates were reduced more among patients undergoing urgent revascularization (9.2% enoxaparin v. 15.4% unfractionated heparin, $p = 0.003$) than among those with nonurgent (1.5% enoxaparin versus 2.7% unfractionated heparin, $p = 0.15$) or without or before revascularization (1.3% enoxaparin v. 1.7% unfractionated heparin, $p = 0.19$). The median time to urgent revascularization was 0 days (interquartile range [IQR] 0–1 days); for nonurgent revascularization, 5 (IQR 2–9) days. Paradoxically, although excess bleeding occurred in both groups undergoing revascularization, the excess rate of major bleeding associated with enoxaparin was greater among patients either not undergoing or before revascularization (2.0% enoxaparin v. 0.9% unfractionated heparin, $p = 0.001$; see online Appendix 3, www.cmaj.ca/cgi/content/full/174/10/1421/DC1). These findings remained unchanged after adjusting for baseline factors (age, sex, diabetes, MI location, heart rate and systolic blood pressure) and use of glycoprotein IIb/IIIa inhibitors, thienopyridines, thrombolytics or heparin.

Fig. 2 shows the predictors of intracranial hemorrhage. Age of 65 years or more, with a progressive incremental risk above 75 years, and systolic blood pressure of 150 mm Hg or higher were significant predictors of intracranial hemorrhage. A tendency toward increased risk was also evident among those treated between 2 and 4 hours after the onset of symptoms of MI. Among women older than 75 years, intracranial hemorrhage was much more common with enoxaparin (10/183 such patients, or 5.5%) than with unfractionated heparin (1/185 or 0.5%; $p = 0.005$). Moreover, the interaction between age, sex and enoxaparin treatment for the occurrence of intracranial hemorrhage was significant ($p = 0.001$). When rates of intracranial hemorrhage were examined by trial and according to treatment (Fig. 3), a significant excess occurred among patients assigned to the enoxaparin group in ASSENT-3 PLUS, but not in ASSENT-3 ($p = 0.005$ for interaction between age, sex, treatment assignment, and trial in the pooled analysis).

Interpretation

This large, pooled analysis comparing 2 antithrombotics used in conjunction with tenecteplase to treat STEMI in over 5700 patients in 2 separate studies demonstrated the substantial therapeutic effect of enoxaparin in the prevention of recurrent MIs and

refractory ischemia in hospital. The new data we have reported here supported an increased benefit of enoxaparin among patients with STEMI who were undergoing revascularization; unexpectedly, most of the bleeding risk was among patients not undergoing revascularization. We also found an important 3-way interaction between age, female sex and enoxaparin that contributed to the risk of intracranial hemorrhage.

An increase in intracranial hemorrhage among patients with STEMI who were treated prehospital with tenecteplase and enoxaparin seems surprising, given that it was not evident in the larger population of patients treated in hospital. Women older than 75 years in the enoxaparin group were at an especially high risk of intracranial hemorrhage. Since patients who summon an ambulance for transport to an emergency department are at higher risk than those who arrive by other means, these observations may relate to differences in these populations.[4,5] Further evidence suggesting that prehospital patients are at greater risk was our finding that 13 of the 97 deaths dur-

ing ASSENT-3 PLUS were prehospital; such data would have been excluded from the ASSENT-3 study. Although this rate of prehospital death was higher than rates reported from recent trials involving patients with STEMI who were transferred from community to tertiary care centres,[6,7] prescreening of severely ill patients may, unlike ASSENT-3 PLUS, have resulted in patient exclusion from those studies. Moreover, patients involved in ASSENT-3 PLUS were far more likely to receive thienopyridine therapy and glycoprotein IIb/IIIa inhibitors. Since 39% of patients assigned to receive unfractionated heparin in ASSENT-3 PLUS did not receive a prehospital infusion after the bolus, and nearly half of them had subtherapeutic initial aPTTs, the differences between the 2 antithrombotic strategies may have been further amplified. Despite a reduction in unfractionated heparin in both the IV bolus and infusion rates undertaken in ASSENT-3 (in accordance with the American College of Cardiology–American Heart Association guidelines for treatment of STEMI), no reduction in intracranial hemorrhage was evident

Outcome	ASSENT trial	UF heparin	Enoxaparin	Odds ratio (95% CI)
Primary efficacy end point	3	314/2038	233/2037	1.41 (1.18-1.69)
	3+	142/818	116/817	1.27 (0.97-1.66)
	Total	456/2856	349/2854	1.36 (1.17-1.59)
Pr. efficacy and safety end point	3	347/2036	280/2037	1.29 (1.09-1.53)
	3+	166/818	149/816	1.14 (0.89-1.46)
	Total	513/2854	429/2853	1.24 (1.08-1.43)
30-day mortality	3	122/2038	109/2137	1.13 (0.86-1.47)
	3+	49/818*	61/817*	0.79 (0.54-1.17)
	Total	171/2856	170/2854	1.01 (0.81-1.25)
Reinfarction	3	86/2038	53/2040	1.65 (1.17-2.34)
	3+	48/821	29/818	1.69 (1.05-2.71)
	Total	134/2859	82/2858	1.67 (1.26-2.20)
Refractory ischemia	3	132/2038	93/2040	1.45 (1.10-1.91)
	3+	53/821	36/818	1.50 (0.97-2.32)
	Total	185/2859	129/2858	1.46 (1.16-1.84)
Intracranial hemorrhage	3	19/2038	18/2040	1.06 (0.55-2.12)
	3+	8/821	18/818	0.44 (0.18-1.01)
	Total	27/2959	36/2858	0.75 (0.45-1.23)
Major bleed	3	44/2035	62/2030	0.71 (0.48-1.04)
	3+	23/821	33/817	0.69 (0.40-1.18)
	Total	67/2856	95/2857	0.70 (0.51-0.96)

UF heparin better ← → Enoxaparin better

*Rates were 5.2% v. 6.8% (odds ratio 0.75, 95% CI 0.50-1.14) when the 13 prehospital deaths were excluded.

Fig. 1: Odds ratios and 95% confidence intervals (CI) for individual and composite efficacy and safety end points for ASSENT-3 (indicated as 3), ASSENT-3 PLUS (3+) and pooled (Total) data. Data are plotted as odds ratios (the dimensions of the boxes represent relative population sizes) with 95% confidence intervals (bars). ASSENT = Assessment of the Safety and Efficacy of a New Thrombolytic Agent, UF = unfractionated, Pr. = primary.
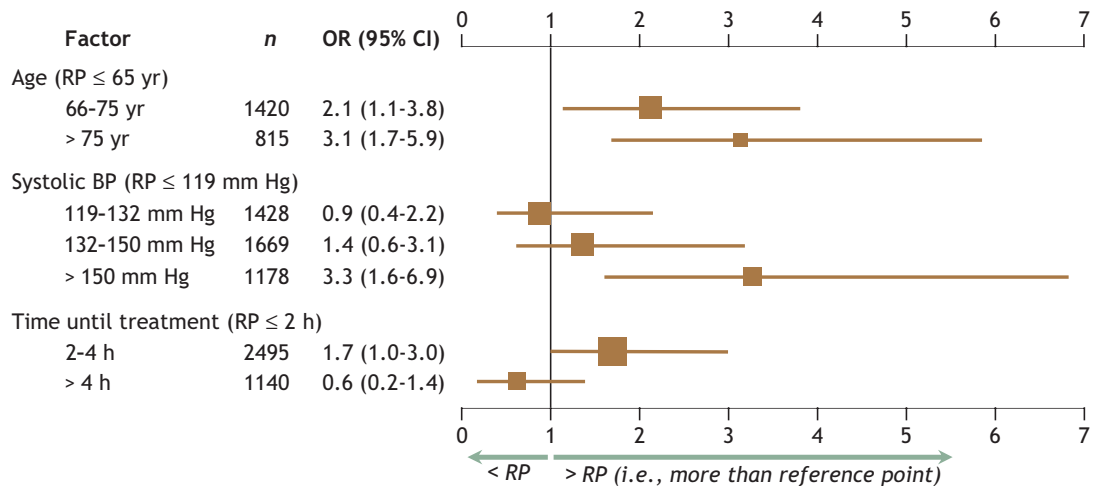
Fig. 2: The main effects, in terms of odds ratios (ORs, shown in the graph as boxes) and 95% confidence intervals (CI, shown as bars), of independent factors predicting the occurrence of intracranial hemorrhage relative to the reference points of age ≤ 65 years, systolic blood pressure ≤ 119 mm Hg and time from symptom onset to treatment ≤ 2 hours (N = 5717). The relative importance of these 3 measures, as indicated by their χ^2 values, is 15, 17 and 10, respectively. There was a 4-way age–sex–treatment–trial interaction (p = 0.005). The area under the receiver–operator curve (AUC index) for this logistic regression was 0.728.
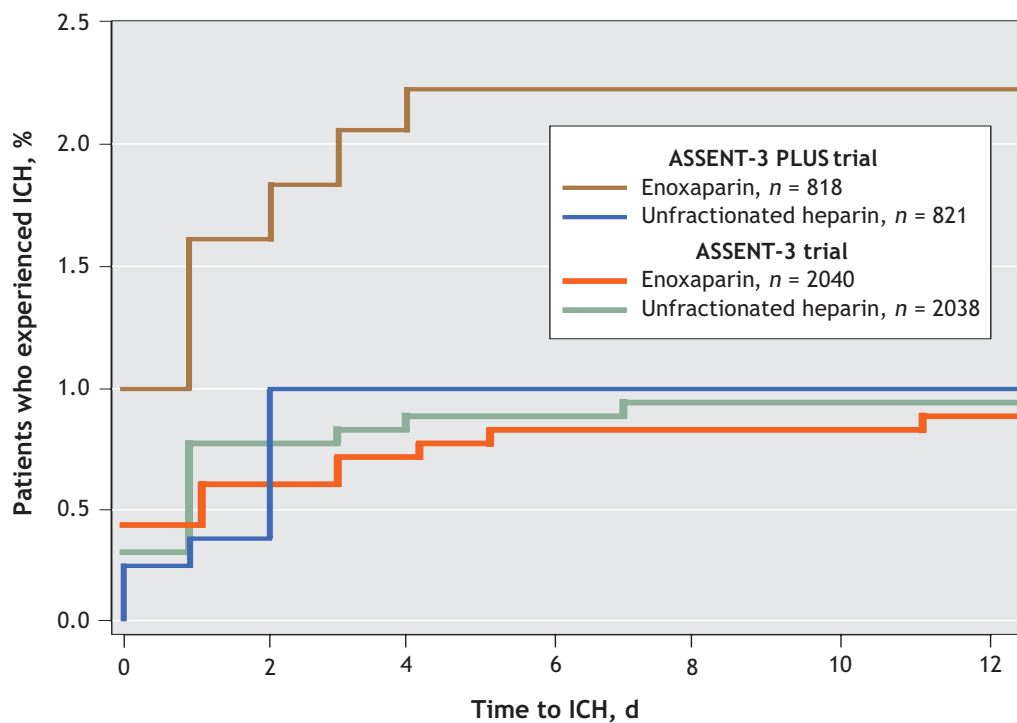
Fig. 3: Cumulative occurrence of intracranial hemorrhage (ICH) by antithrombotic treatment group. Data from the enoxaparin group from the ASSENT-3 PLUS trial were compared with those from the ASSENT-3 trial (p = 0.01), and with data from the unfractionated heparin groups of the ASSENT-3 PLUS (p = 0.047) and ASSENT-3 (p = 0.004) trials, by means of the log–rank test.

over the more aggressive antithrombotic heparin strategy in ASSENT-2.[1,8,9] About 1 in 5 patients who were randomly assigned prehospital to a treatment group were not assigned a Killip class; this, along with our inability to discern which patients in ASSENT-3 arrived by ambulance, somewhat limits our intertrial comparison and suggests a need for caution in interpreting the effects on intracranial hemorrhage in the ASSENT-3 PLUS trial.

A consistent benefit in avoidance of reinfarction and refractory recurrent ischemia among patients treated with enoxaparin was evident in both trials. We report a novel insight into a partitioning of treatment effect among those 1 in 5 patients (18%) undergoing urgent revascularization. This amplification of treatment benefit in a high-risk group that otherwise exhibits a higher rate of recurrent MI is consistent with the benefit amplification that occurs when glycoprotein IIb/IIIa inhibitors are used in conjunction with revascularization in non–ST-segment elevation acute coronary syndromes.[10] The intervals until myocardial reinfarction or revascularization were recorded only in days; since 65% of reinfarctions (110/168) occurred on the same day as revascularization, we cannot evaluate what proportion of reinfarctions led to urgent revascularization versus those that resulted from invasive procedures. Our post hoc subgroup analyses therefore require further validation.[11] Notwithstanding this benefit in patients who underwent revascularization, the increased frequency of major systemic bleeding among nonrevascularized patients over the duration of the hospital stay raises a question as to whether the duration of enoxaparin therapy is appropriately balanced with the risk–benefit ratio. Since the majority of recurrent infarctions, refractory ischemia and urgent revascularizations occur soon after presentation, it may be prudent to further explore the optimal duration of enoxaparin therapy.

In summary, our pooled analysis of ASSENT-3 and ASSENT-3 PLUS data showed that the combination of tenecteplase and enoxaparin was associated with a robust reduction in reinfarction and refractory ischemia, augmentation in major systemic bleeding and a propensity for increased intracranial hemorrhage among elderly patients (> 75 years), especially women.[12] This last finding suggests not only a need for caution but also a need for further studies involving this growing segment of the population, which has high rates of adverse events after treatment of STEMI.

Since acceptance of our article for publication, findings from the ExTRACT (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction) trial, a large study of fibrinolysis after STEMI that compared enoxaparin (a reduced dose, in patients over the age of 75) with unfractionated heparin, have been published.[13] Those investigators also found a a reduction in the overall risk of death and nonfatal reinfarction with enoxaparin, associated with an increased risk of major bleeding but without any significant increase in risk of intracranial hemorrhage.

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