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Enoxaparin vs. unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction in elderly and younger patients: results from ExTRACT-TIMI 25

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Age

Aims To determine the effects of age on outcomes in patients with STEMI treated with a strategy of enoxaparin (ENOX) vs. unfractionated heparin (UFH).
Methods and results In the ExTRACT-TIMI 25 trial, 20 479 patients with STEMI were randomized in a double-blind fashion to UFH or ENOX. A novel reduced dose of ENOX was administered to patients ≥ 75 years, and a reduced dose in those with an estimated creatinine clearance of < 30 mL/min. Anti-Xa levels were measured in a subset of patients ($n = 73$). The exposure to anti-Xa over time was lower in the elderly (AUC_{0-12h} $P < 0.0001$; $AUC_{steady\text{-}state}$ $P = 0.0046$). The relative risk reduction (RR) with ENOX on the primary endpoint, i.e. death or non-fatal recurrent myocardial infarction, was greater in patients < 75 years (20%) than > 75 years (6%), but the absolute benefits were similar. When compared with UFH, ENOX was associated with an RR of 1.67 for major bleeding, but the magnitude of the excess risk tended to be lower (RR = 1.15) in patients ≥ 75 years assigned to ENOX.
Conclusion A dose reduction of ENOX in the elderly appears to be helpful in ameliorating bleeding risk. A strategy of ENOX was superior to UFH in both young and elderly patients with STEMI treated with fibrinolysis.

Introduction

ST-segment elevation myocardial infarction (STEMI) occurs most frequently in patients ranging from the fourth to the ninth decades, peaking in the seventh and eight decades. Elderly patients are the fastest growing segment of the population, and they make up an increasing proportion of patients who suffer from STEMI.[1] It is well established that age is an important determinant of the outcome of STEMI.[2] Indeed, patients > 75 years account for over one-half of the mortality from this condition and they are more likely to experience complications of myocardial infarction (MI), such as heart failure, stroke, and re-infarction.[3] In addition, the elderly are more likely to have adverse events related to treatments, including bleeding with anti-thrombotic therapies.

Despite progressively impaired renal function with ageing,[4] little attention has been paid to dose adjustment of anti-thrombotic therapies. This is of particular importance in the management of drugs such as enoxaparin (ENOX) in which the anti-IIa activity is cleared by non-renal mechanisms and the anti-Xa activity is cleared renally. Earlier studies had shown increased bleeding with ENOX in elderly MI patients.[5,6] In the ExTRACT-TIMI 25 trial, a novel modified dosing regimen of ENOX was tested in patients aged ≥ 75 years.[7,8] The results of the trial focusing on the effects of this dose adjustment in the elderly are reported.

Methods

Patient population and protocol

The study design[7] and primary results of ExTRACT-TIMI 25 have been published.[8] In brief, 20 479 patients from the intention-to-treat (ITT) cohort of the trial were randomized in 674 sites in 48 countries. Entry criteria included ischaemic symptoms within 6 h of randomization with ST-segment elevation or left bundle branch block. Contraindications included serum creatinine > 2.5 mg/dL (> 220 μmol/L) for men and > 2.0 mg/dL (> 175 μmol/L) for women. The fibrinolytic was selected at the discretion of the treating physician and all patients were to receive aspirin. Subjects were randomized either to the standard anti-thrombin strategy with unfractionated heparin (UFH) or to an ENOX strategy. UFH (or matching placebo) was administered to all patients assigned to this strategy with an i.v. bolus of 60 U/kg body weight (4000 U maximum) followed by an infusion of 12 U/kg/h (maximum 1000 U/h) for at least 48 h, with adjustment to an activated

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partial thromboplastin time of 1.5–2.0× control. ENOX (or matching placebo) was given to patients <75 years as a 30 mg i.v. bolus followed by 1.0 mg/kg subcutaneously every 12 h. For patients ≥75 years, a modified dosing regimen was tested with omission of the i.v. bolus and reduction of the maintenance dose to 0.75 mg/kg subcutaneously every 12 h until hospital discharge or 8 days. For patients of any age with an estimated creatinine clearance (CrCl) of <30 mL/min, the dose was modified to 1.0 mg/kg every 24 h. CrCl was estimated by the Cockcroft–Gault formula.[9] The estimation of CrCl occurred after the serum creatinine measurement from admission was available. This allowed investigators sufficient time to determine if the second subcutaneous injection of ENOX was to be administered either 12 h or 24 h after the initial injection.

The primary endpoint was death or non-fatal MI at 30 days. Bleeding was classified according to the TIMI criteria.[2,7,9]

Pharmacokinetic analyses

The modifications in the ENOX dosing regimen described above for elderly patients and those with severe renal dysfunction (e.g. CrCl <30 mL/min) were based on pharmacokinetic modelling in previous studies.[10,11] Body weight and renal function are significantly related to the clearance of anti-Xa activity following ENOX administration. In addition, clearance of anti-Xa activity closely correlates with the risk of bleeding.[10] Anticipating that elderly patients have reduced CrCl, the initial i.v. bolus of ENOX was eliminated (to avoid excessive anti-Xa activity when the lytic effect was highest) and the maintenance dose was reduced by 25% to 0.75 mg/kg subcutaneously every 12 h. Since prior studies showed that there was a marked reduction in the clearance of anti-Xa activity in patients with a CrCl <30 mL/min, the dosing interval was widened and the subcutaneous regimen was 1.0 mg/kg every 24 h.[10] The goal of the dose modifications in the elderly and severe renal dysfunction patients was to reduce the exposure to anti-Xa activity because of excessive accumulation over time.

On the basis of the pharmacokinetic model developed in the TIMI 11A Study, a sparse sampling strategy was designed as a substudy in the ExTRACT-TIMI 25 trial.[10] Two samples were collected per patient, as described previously, after the first subcutaneous dose of ENOX, one between 0.5 and 2.5 h and the other between 4 and 12 h.[10,11] Given the plans for a sparse sampling strategy, the pharmacokinetic substudy was conducted in 39 sites from nine countries and was open to all eligible patients for the trial at those sites who consented to the additional blood specimens.

Statistical analysis

All efficacy analyses were based on the ITT principle. The ITT cohort was prespecified to include all patients randomized for whom follow-up information was available. Safety analyses were performed according to the treatment actually received. Continuous variables are presented as median and interquartile range (IQR), and categorical variables as frequencies. In the comparison of baseline characteristics stratified by young (<75 years) and elderly (≥75 years) age groups, differences in categorical variables were analysed using the χ^2 test. Risk ratios (RR) and the corresponding 95% CIs are reported for the comparisons of ENOX:UFH for the given subgroups analysed. The frequency of efficacy and safety outcomes at 30 days in the two age strata were compared with the χ^2 test. Logistic regression was performed to evaluate the interaction between age group and randomized treatment. All *P*-values reported are two-sided and performed at $\alpha = 0.05$ significance level. Because of the exploratory nature of the analysis, *P*-values are not adjusted for multiplicity. All statistical analyses were performed using Stata/SE, version 9.1 (StataCorp, College Station, TX, USA).

Results

Effect of age on baseline characteristics

Baseline characteristics varied substantially in relation to age (*Table 1*). Compared with the 17 947 patients <75 years, the 2532 patients ≥75 years (representing 12.4% of the ITT population) had a higher prevalence of hypertension and diabetes, but were less likely to be current smokers. Elderly patients were significantly more likely to have had a prior MI, history of angina pectoris, and be receiving long-term treatment with aspirin. They were also at significantly higher risk of poor outcomes from STEMI as assessed by Killip Class, TIMI Risk Score, and TIMI Risk Index. Of note, the CrCl was markedly lower in elderly patients. Within each age stratum, the patients assigned to the ENOX and UFH strategies were well matched with no significant differences in baseline characteristics (data not shown). Among the patients <75, the median CrCl was 86.7 (69.1, 108.1) mL/min in those assigned to ENOX ($n = 9015$) and was 86.8 (68.1, 107.6) mL/min assigned to UFH ($n = 8932$). Among the patients ≥75, the median CrCl was 51.9 (41.9, 64.7) mL/min in those assigned to ENOX ($n = 1241$) and 52.1 (41.6, 65.0) mL/min in those assigned to UFH ($n = 1291$).

Effect of age on treatments received

The use of aspirin and beta-blockers (both recommended in the protocol in the absence of contraindications) were significantly lower in elderly when compared with younger patients (*Table 1*). Other medications, shown to reduce events after STEMI in prior trials, including clopidogrel, inhibitors of the renin–angiotensin system, and statins were also used less frequently in elderly patients. As for the baseline characteristics, no differences were noted between the patients assigned to ENOX or UFH within the two age strata.

Anti-Xa results

A total of 73 patients were included in the pharmacokinetic substudy reported here: 60 were <75 years and 13 were ≥75 years. The mean clearance of anti-Xa activity in patients <75 years was 0.794 L/h and was reduced by 17.6% to 0.654 L/h in patients ≥75 years ($P = 0.049$). The area under the concentration time curve (AUC) from 0 to 12 h was a median of 9839 (8295, 11 579) I·U·h/L in the young patients and 4532 (3816, 6540) ($P < 0.001$), reflecting the lack of administration of the i.v. bolus in the elderly patients. At steady-state, the AUC was 10 000 (8499, 10926) I·U·h/L in the young patients and 8197 (7395, 8798) in the elderly patients ($P = 0.0046$), reflecting a significantly lower rate of accumulation of anti-Xa in the elderly patients over time.

Outcome by treatment assignment

The rate of death or non-fatal recurrent MI at 30 days was significantly lower in patients <75 years treated with ENOX (7.9% vs. 9.9%; RR 0.80; 0.72–0.87, $P < 0.0001$) (*Figure 1*). This endpoint also tended to occur less frequently with ENOX in patients ≥75 years (24.8% vs. 26.3%; RR 0.94; 0.82–1.08; $P_{\text{interaction}} = 0.10$). The absolute risk difference in favour of ENOX was 2.0% in patients <75 years and 1.5% in those ≥75 years (*Figure 1*). These

Table 1 Baseline characteristics of patients in young and elderly age groups

Characteristic	Age < 75 ($n = 17\,947$)	Age ≥ 75 ($n = 2\,532$)	*P*-value
Male sex, no. (%)	14 368 (80.1)	1 328 (52.5)	<0.001
White race, no./total no. (%)	15 470/17 946 (86.2)	2 385/2 532 (94.2)	<0.001
Weight (kg)			<0.001
Median	78	70	
Interquartile range	70, 86	62, 79.1	
Hypertension, no./total no. (%)	7 419/17 728 (41.9)	1 487/2 505 (59.4)	<0.001
Hyperlipidaemia, no./total no. (%)	2 562/13 973 (18.3)	355/1 996 (17.8)	0.6
Current smoker, no./total no. (%)	9 386/17 943 (52.3)	306/2 526 (12.1)	<0.001
Prior MI, no./total no. (%)	2 169/17 890 (12.1)	490/2 514 (19.5)	<0.001
Prior angina pectoris, no./total no. (%)	4 695/17 833 (26.3)	1 020/2 512 (40.6)	<0.001
Prior PCI, no./total no. (%)	597/17 933 (3.3)	63/2 528 (2.5)	0.026
Anterior MI, no./total no. (%)	7 714/17 853 (43.2)	1 219/2 480 (49.2)	<0.001
Diabetes mellitus	2 607/17 739 (14.7)	453/2 510 (18.1)	<0.001
Long-term treatment w/aspirin, no./total no. (%)	2 190/17 916 (12.2)	562/2 520 (22.3)	<0.001
UFH within 3 h before randomization, no./total no. (%)	2 885/17 947 (16.1)	357/2 531 (14.1)	0.011
LMWH within 7 days before randomization, no./total no. (%)	67 (0.4)	26 (1.0)	<0.001
Creatinine clearance (mL/min)			<0.001
Median	86.7	54.5	
Interquartile range	68.6, 107.9	41.9, 64.8	
Creatinine clearance, no./total no. (%)			<0.001
<30 mL/min	87/16 265 (0.5)	145/2 313 (6.3)	
30–60 mL/min	2 272/16 265 (14.0)	1 399/2 313 (60.5)	
>60 mL/min	13 906/16 265 (85.5)	769/2 313 (33.3)	
Killip Class, no. (%)			<0.001
I	16 157/17 938 (90.1)	2 019/2 530 (79.8)	
II	1 629/17 938 (9.1)	456/2 530 (18.0)	
III	142/17 938 (0.8)	51/2 530 (2.0)	
IV	10/17 938 (0.1)	4/2 530 (0.2)	
TIMI risk score, no./total no. (%)			<0.001
≤3	12 942/17 776 (72.8)	111/2 500 (4.4)	
>3	4 834/17 776 (27.2)	2 389/2 500 (95.6)	
TIMI risk index, no./total no. (%)			<0.001
≤12.5	3 445/17 498 (19.7)	0/2 443 (0.0)	
>12.5–17.5	4 650/17 498 (26.6)	4/2 443 (0.2)	
>17.5–22.5	3 969/17 498 (22.7)	98/2 443 (4.0)	
>22.5–30	3 554/17 498 (20.3)	572/2 443 (23.4)	
>30	1 880/17 498 (10.7)	1 769/2 443 (72.4)	
Time from symptom onset to start of fibrinolytic therapy (h)			<0.001
Median	3.1	3.3	
Interquartile range	2.2, 4.3	2.4, 4.5	
Fibrinolytic therapy, no. (%)			<0.001
Tenecteplase	3 388 (18.9)	598 (23.7)	
Alteplase	10 015 (56.0)	1 160 (45.9)	
Reteplase	968 (5.4)	154 (6.1)	
Streptokinase	3 524 (19.7)	615 (24.3)	
Cardiac medications during index hospitalization, no. (%)			
Aspirin	17 250 (96.1)	2 226 (87.9)	<0.001
Clopidogrel	5 213 (29.1)	514 (20.3)	<0.001
Beta-blockers	15 606 (87.0)	1 950 (77.0)	<0.001
ACE-inhibitors or angiotensin-receptor blockers	14 362 (80.0)	1 955 (77.2)	0.001
Statin	12 736 (71.0)	1 491 (58.9)	<0.001

differences translate into a number needed-to-treat (NNT) in order to prevent one event of 50 in patients <75 years treated and 67 in patients ≥75 years.

The rate of the prespecified major secondary endpoint, death, or non-fatal re-infarction or urgent revascularization occurred in 12.4% of UFH patients and 9.7% of ENOX patients <75 years (RR 0.78, CI 0.72–0.85, $P < 0.001$) and in 28.4% of UFH patients and 26.0% of ENOX patients ≥75 years (RR 0.92; CI 0.81–1.04, $P = 0.18$; $P_{\text{interaction}} = 0.12$) (*Figure 1*). The absolute risk difference in favour of ENOX was 2.7% in patients <75 years and 2.5% in those ≥75 years, corresponding to NNT calculations of 37 and 42, respectively, to prevent one secondary endpoint.

The rate of all-cause mortality was 5.5% in the UFH patients and 5.0% in the ENOX patients <75 years (RR 0.90, CI 0.80–1.02) and was 21.2% in the UFH patients when compared with 21.0% in the ENOX patients ≥75 years (RR 0.99, CI 0.85–1.15; $P_{\text{interaction}} = 0.45$).

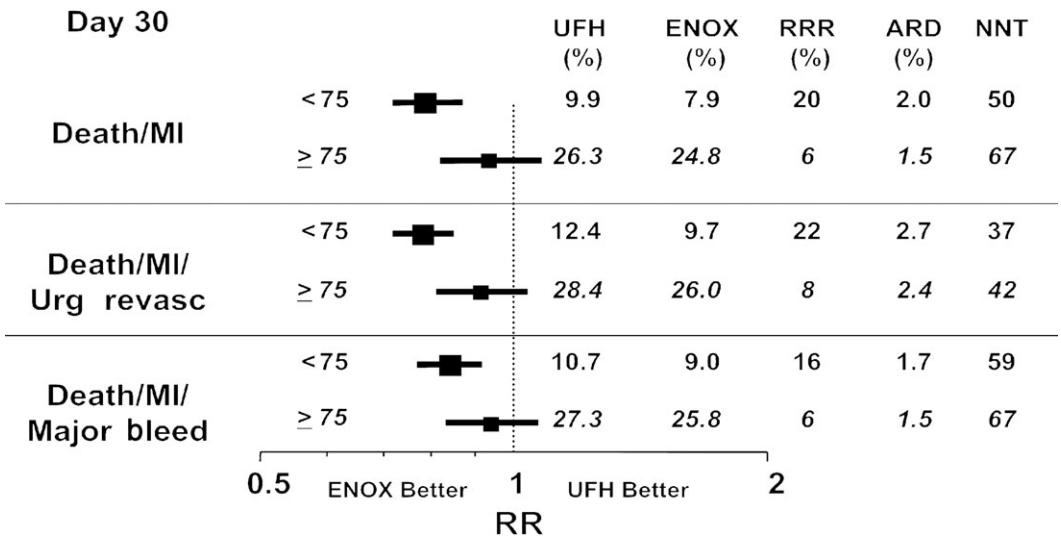

Figure 1 Treatment effects of enoxaparin stratified by age cut-off of 75 years. There were 17 947 patients <75 and 2532 patients ≥75 years. ARD, absolute risk difference; ENOX, enoxaparin; MI, myocardial infarction; NNT, number needed-to-treat; RRR, relative risk reduction; UFH, unfractionated heparin; Urg revasc, urgent revascularization. The squares (proportional to sample size) depict the point estimates for the relative risk and width of the horizontal lines depicts the 95% CI.

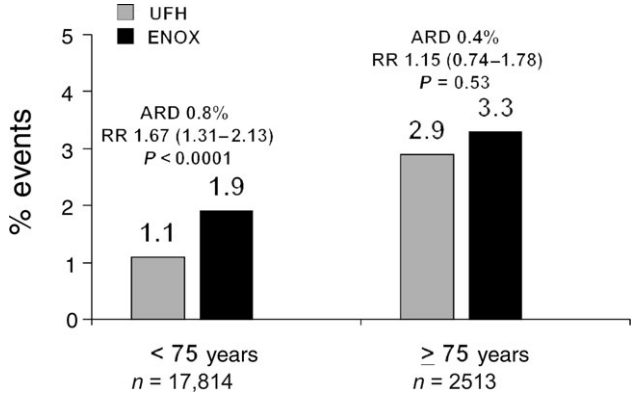

Figure 2 TIMI Major bleeding at 30 days stratified by age cut-off of 75 years. Abbreviations as in *Figure 1*.

Major bleeding occurred in 1.1% of UFH vs. 1.9% of ENOX patients <75 years (RR 1.67, 95% CI 1.31–2.13, $P < 0.0001$) and 2.9% UFH vs. 3.3% ENOX (RR = 1.15, 95% CI 0.74–1.78, $P = 0.53$), in patients ≥75 years ($P_{interaction} = 0.16$) (*Figure 2*). Although the incidence of intracranial haemorrhage was higher in the elderly, there were no significant differences between the UFH and ENOX groups in each of the two age strata: 0.5% vs. 0.7%, $P = 0.06$ in patients <75 years and 1.7% vs. 1.6% $P = 0.85$ in patients ≥75 years. Among patients with a major bleed, death with primary cause attributed to haemorrhage or intracranial haemorrhage occurred in 1.3% of both the UFH and ENOX group among patients ≥75 years and in 0.2% of the UFH and 0.45% of the ENOX group among patients <75 years.

Net clinical benefit

The net clinical benefit endpoint (death or non-fatal re-infarction or non-fatal major bleeding) rate was 10.7% in UFH patients and 9.0% of ENOX patients <75 years (RR 0.84; 95% CI 0.77–0.92; $P < 0.001$) and was 27.3% and 25.8%, respectively, in the patients ≥75 years (RR 0.94; 95% CI 0.83–1.07; $P = 0.38$; $P_{interaction} = 0.28$). The absolute risk difference in favour of ENOX was 1.7% in patients <75 years and 1.5% in those ≥75 years, corresponding to NNT to prevent one event of 59 and 67, respectively (*Figure 1*). A comparison of the treatment effects of ENOX for every 1000 patients treated, stratified by the age cutpoint of 75 years is shown in *Figure 3*.

Discussion

We tested a novel ENOX dosing regimen in patients ≥75 years and the findings stratified by age <75 years vs. ≥75 years are of interest. Although the relative RR of the primary endpoint with ENOX was greater in the <75 vs. ≥75 year-old cohorts (20% vs. 6%), because of the higher absolute event rates in the elderly, the absolute risk differences favoured ENOX in both age cohorts (2.0% vs. 1.5%). The NNT to prevent one primary endpoint event were similar in the younger and older cohorts (*Figure 1*).

The relative increase in major bleeding that was seen with ENOX in the patients ≥75 years (RR = 1.15) was less than in patients <75 years (RR = 1.67) (*Figure 2*) and the rates of intracranial haemorrhage in patients ≥75 years were similar in the UFH and ENOX groups. We speculate that this trend to a reduced relative rate of excessive bleeding with ENOX in the elderly compared with the young may be a consequence of omission of the i.v. bolus loading dose and reduction in the maintenance dose of ENOX in patients ≥75 years. In support of this hypothesis are the anti-Xa results that showed significantly lower rates of exposure to anti-Xa activity both between 0 and 12 h and at steady state in the elderly patients. In addition, the protocol mandated modification of the maintenance dose of ENOX to 1.0 mg/kg every 24 h for patients with a CrCl of <30 mL/min and this may also have played a role in limiting the excess bleeding in the elderly patients in whom renal dysfunction occurred more frequently. While advanced age, diminished renal function, and low body weight have all been shown to relate to increased bleeding risk, the

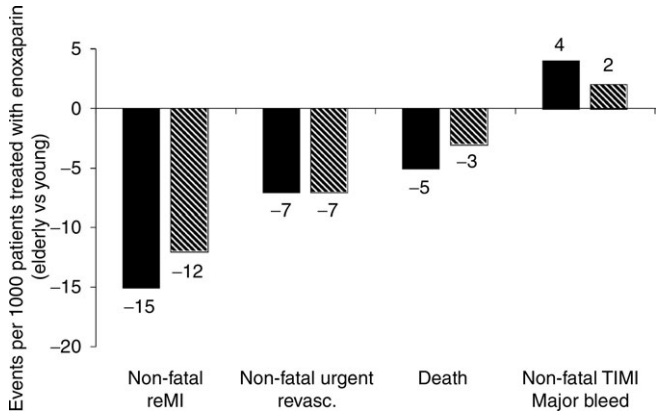

Figure 3 Impact of ENOX on key outcomes for every 1000 patients treated, stratified by age cut-off of 75 years. Patients <75 are plotted to the left in each pair of bars while those ≥75 years are plotted to the right.

relative contribution of each of these inter-related factors is difficult to assess and likely varies from patient to patient.

The rates of major bleeds in young and old patients with STEMI are of considerable clinical interest. Although the absolute rates were lower in the younger patients in ExTRACT-TIMI 25, it is of note that there was a significant relative excess of bleeds in younger patients treated with enoxaparin (*Figure 2*). This underscores the need for additional studies to define further the optimal ENOX dosing regimen in younger patients, who may benefit from a lower exposure to anti-Xa activity than was achieved in this trial.

With respect to patients ≥75 years, the findings of ExTRACT-TIMI 25 represent an important advance when compared with prior studies. In the 4078 patients in the ASSENT 3 trial,[5] in patients with STEMI treated with tenecteplase, and randomized to receive UFH or ENOX regimens, similar to those used in patients <75 years in ExTRACT-TIMI 25, the rates of major bleeding increased from 1.8% (UFH) vs. 2.4% (ENOX) in patients aged ≤75 years to 4.1% (UFH) vs. 13.3% (ENOX), in patients aged >75 years. There also was an increase in the incidence of intracranial haemorrhage in patients treated with ENOX in patients >75 years: 0.74% (UFH) vs. 1.54% (ENOX).[12] In the 1639 patients randomized to the ASSENT-3 PLUS trial,[6] which compared UFH and ENOX as an adjunct to tenecteplase administered in the prehospital phase, the rate of intracranial haemorrhage was 0.8% (UFH) and 6.7% (ENOX) in patients >75 years ($P = 0.01$). The investigators hypothesized that this increase in intracranial haemorrhage in older patients may have been due to higher blood pressures in the early stages of STEMI, more frequent use of clopidogrel, IIb/IIIa antagonists, non-therapeutic dosing of UFH and ENOX, more dosing errors with tenecteplase, and more coronary procedures in patients treated during pre-hospitalization. Of note, both the rates of major bleeding and intracranial haemorrhage in patients ≥75 years in ExTRACT-TIMI 25 treated with the modified doses of ENOX were lower than that reported in the ASSENT-3 and ASSENT-3 PLUS trials.

Conclusion

In patients with STEMI treated with fibrinolytic therapy, the modified (reduced) dosing regimen of ENOX in patients ≥75 years appears to have been helpful in reducing the magnitude of the relative increase in major bleeding, including the intracranial haemorrhage that has been observed in this age group in previous trials. The similar ARD and NNT in the elderly and young patients suggest that the reduced ENOX dose in the elderly did not compromise its efficacy in preventing death or MI. Thus, the ENOX strategy as implemented in ExTRACT-TIMI 25 is preferred to the standard UFH strategy in both younger and older STEMI patients treated with fibrinolysis.

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Clinical vignette

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Saphenous vein graft aneurysm

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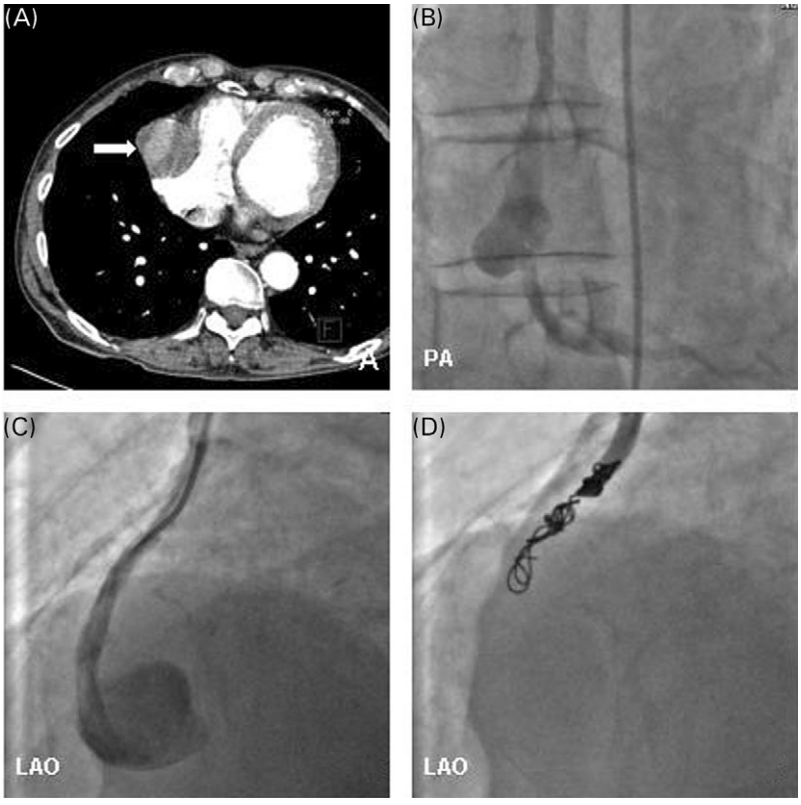
An 80-year-old man with chronic stable angina and a history of coronary artery bypass grafting underwent contrast-enhanced computed tomography for investigation of aorto-iliac disease. As an incidental finding, he was noted to have a large coronary vein graft aneurysm adjacent to the right heart (Panel A). Coronary angiography 2 years previously had demonstrated a patent internal mammary artery to the left anterior descending artery and a patent vein graft to the right coronary artery with aneurysmal dilatation of the distal vein graft (Panel B). No intervention was undertaken at that time.

Angiography on this occasion demonstrated considerable expansion of the vein graft aneurysm with no perceivable distal run-off (Panel C). Prolonged occlusion of the vein graft proximally with a 5×15 mm Maverick angioplasty balloon (Boston Scientific, Maple Grove, MN, USA) resulted in neither symptomatic nor electrocardiographic evidence of myocardial ischaemia. In the absence of a distal lumen, percutaneous closure of the aneurysm using covered stents was not possible and vein graft occlusion was achieved following deployment of two Nester 6 mm×14 cm coils (Cook, Bloomington, Ind., USA) within the proximal segment of the vein graft (Panel D).



Aneurysmal dilatation of saphenous vein grafts is uncommon but is associated with significant in-hospital mortality largely due to graft rupture. This case highlights the importance of early treatment of vein graft aneurysms. Closure of the aneurysm when it was first identified, using covered stents, might have prevented graft enlargement, removing the risk of graft rupture and preserving graft patency and distal run-off.

Panel A. Contrast-enhanced computed tomography demonstrating an aneurysm of the right coronary vein graft (arrow).

Panel B. Angiogram performed 2 years earlier demonstrating aneurysmal dilatation of the vein graft to the right coronary artery with good distal run-off.

Panel C. Angiogram performed on this occasion demonstrating significant enlargement of the aneurysm with absent distal run off.

Panel D. Angiogram obtained immediately following coiling of the neck of the vein graft. Complete occlusion of the graft has been achieved.