Safety and effectiveness of enoxaparin following fibrinolytic therapy: Results of the Acute Myocardial Infarction (AMI)-QUEBEC registry

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BACKGROUND: Previous randomized controlled trials and meta-analyses demonstrated the superior efficacy of enoxaparin (ENOX) over unfractionated heparin (UFH) in patients with ST segment elevation myocardial infarction (STEMI). The external validity of randomized controlled trials may be limited by selective inclusion of patients who are younger and healthier than the 'real-life' population.

OBJECTIVE: To evaluate the safety and effectiveness of ENOX compared with UFH in unselected STEMI patients.

METHODS: The safety and effectiveness of ENOX and UFH were compared in STEMI patients who received fibrinolytic therapy at 17 Quebec hospitals in 2003.

RESULTS: A total of 498 STEMI patients received systemic anticoagulation, with ENOX and UFH administered in 114 and 384 patients, respectively. There were no differences in baseline characteristics between the two patient groups. The rates of in-hospital major adverse cardiac or cerebral events were 11.4% in the ENOX group compared with 14.0% in the UFH group ($P=0.51$). In-hospital death or nonfatal reinfarction occurred in 7.9% of patients who received ENOX compared with 9.9% of patients who received UFH ($P=0.52$). Major bleeding occurred in 4.4% of patients who received ENOX versus 6.0% in patients who received UFH ($P=0.51$).

INTERPRETATION: There was no significant difference in the rates of in-hospital adverse events in the ENOX group compared with the UFH group, when used in the real-life context. Larger observational studies may further confirm the safety, effectiveness and optimal duration of the administration of ENOX in unselected STEMI patients treated with fibrinolysis.

Key Words: Acute myocardial infarction; Anticoagulation; Fibrinolytic therapy

Systemic anticoagulation is recommended following fibrinolytic therapy to maintain coronary artery patency in patients with ST elevation myocardial infarction (STEMI) (1). Although unfractionated heparin (UFH) is commonly administered to STEMI patients, low molecular weight heparin (LMWH) has several potential advantages over UFH that include lesser inhibition by platelet factor 4; greater inhibition of thrombin generation with a higher anti-Xa:IIa ratio; and more potent suppression of von Willebrand factor. Finally, its more predictable dose response and its ease of administration make LMWH a simpler and more convenient anticoagulant than UFH (2,3) following fibrinolytic therapy.

L'innocuité et l'efficacité de l'énoxaparine après une thérapie aux fibrinolytiques : Les résultats du registre québécois d'infarctus aigu du myocarde (IAM)

HISTORIQUE : Des essais aléatoires et contrôlés et des méta-analyses passés ont démontré l'efficacité supérieure de l'énoxaparine (ENOX) par rapport à l'héparine non fractionnée (HNF) chez les patients ayant un infarctus du myocarde avec élévation du segment ST (IMÉST). La validité externe des essais aléatoires et contrôlés peut être limitée par l'inclusion sélective de patients qui sont plus jeunes et en meilleure santé qu'au sein de la « véritable » population.

OBJECTIF : Évaluer l'innocuité et l'efficacité de l'ENOX par rapport à l'HNF chez des patients non sélectionnés ayant eu un IMÉST.

MÉTHODOLOGIE : Les chercheurs ont comparé l'innocuité et l'efficacité de l'ENOX et de l'HNF chez des patients qui ont subi un IMÉST et ont reçu des fibrinolytiques dans 17 hôpitaux québécois en 2003.

RÉSULTATS : Au total, 498 patients ayant subi un IMÉST ont reçu des anticoagulants systémiques, l'ENOX et l'HNF ayant été administrés chez 114 et 384 patients, respectivement. On ne constatait aucune différence à l'égard des caractéristiques de base des deux groupes de patients. Le taux d'événements cardiaques ou cérébraux négatifs majeurs en milieu hospitalier s'élevait à 11,4 % au sein du groupe prenant de l'ENOX, par rapport à 14,0 % dans celui prenant de l'HNF ($P=0,51$). Un décès en milieu hospitalier ou un infarctus non fatal s'est produit chez 7,9 % des patients qui avaient reçu de l'ENOX par rapport à 9,9 % de ceux qui avaient reçu de l'HNF ($P=0,52$). Des saignements majeurs se sont produits chez 4,4 % des patients qui avaient reçu de l'ENOX et 6,0 % de ceux qui avaient reçu de l'HNF ($P=0,51$).

INTERPRÉTATION : En milieu réel, on ne remarquait aucune différence significative dans les taux de réactions néfastes en milieu hospitalier au sein du groupe prenant de l'ENOX par rapport à celui prenant de l'HNF. De plus vastes études d'observation pourraient mieux confirmer l'innocuité, l'efficacité et la durée optimale de l'administration d'ENOX chez des patients non sélectionnés ayant eu un IMÉST et étant traités par fibrinolyse.

The superior efficacy of enoxaparin (ENOX) over UFH has been demonstrated in several STEMI randomized controlled trials and meta-analyses (4-13). However, the external validity of these studies is generally limited, with patients enrolled in clinical trials being generally healthier and younger than 'real-life' patients (14-17). In the real-life context, many drugs may also be less optimally administered than within the ideal conditions of randomized controlled trials (RCTs). Therefore, we aimed to evaluate the safety and effectiveness of ENOX and UFH, combined with fibrinolytic therapy in a cohort of unselected STEMI patients.

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TABLE 1
Comparison of characteristics of patients with and without data on survival status

Characteristics	Data on survival status		P
	Available (n=498)	Missing (n=102)	
Age, years, mean $\pm$ SD	60.3 $\pm$ 12	54.6 $\pm$ 11	0.006
Female sex, %	27.9	22.0	0.53
Diabetes, %	12.1	24.4	0.04
Previous percutaneous coronary intervention, %	8.1	17.1	0.18
Previous cerebrovascular disease, %	3.2	0.0	0.25
Previous myocardial infarction, %	11.1	19.5	0.08
Previous CABG surgery, %	2.6	4.9	0.43
Heart rate at presentation, beats/min, mean $\pm$ SD	74 $\pm$ 20	69 $\pm$ 13	0.04
Systolic blood pressure at presentation, mmHg, mean $\pm$ SD	138 $\pm$ 31	130 $\pm$ 24	0.09
Killip class, mean $\pm$ SD	1.23 $\pm$ 0.65	1.07 $\pm$ 0.26	0.17
TIMI risk index, mean $\pm$ SD	21.3 $\pm$ 9	17.1 $\pm$ 11	0.009
TIMI risk score, mean $\pm$ SD	2.12 $\pm$ 2.4	1.07 $\pm$ 1.9	0.01

Thrombolysis in Myocardial Infarction (TIMI) risk index: heart rate $\times$ [age/10]²/systolic blood pressure. CABG Coronary artery bypass graft

METHODS

The design of the main Acute Myocardial Infarction (AMI)-QUEBEC study has been reported previously (18). In brief, AMI-QUEBEC was a cohort study of patients admitted to 17 Quebec hospitals with a final discharge diagnosis of STEMI from January 1 to December 31, 2003. Approval of the study was obtained from the directors of professional services or institutional review boards at the hospitals that participated.

All consecutive patients with STEMI as the final discharge diagnosis and with a symptom duration of less than 12 h were included. All patients who developed STEMI as an in-hospital complication, or with a symptom duration of more than 12 h, or previous STEMI already captured in the AMI-QUEBEC registry, and those who did not receive reperfusion therapy were excluded. For the purpose of the present study, only patients who received fibrinolytic therapy were included.

End point definitions

The primary end point of major adverse cardiac or cerebral event (MACCE) was a composite of all-cause mortality or nonfatal reinfarction, nonfatal stroke or nonfatal major bleeding complication (intracranial bleed, major bleeding excluding intracranial bleed or transfusion). The effectiveness and safety end points were also examined separately. The primary effectiveness end point was the composite of all-cause mortality or nonfatal reinfarction during the index hospitalization. Diagnosis of reinfarction required a new increase of cardiac biomarkers and confirmation by the treating physician. The primary safety end point was a composite of intracranial bleed, Thrombolysis in Myocardial Infarction (TIMI) major bleed (19) (excluding intracranial bleed) or transfusion of red blood cells. Other safety events of interest were stroke and TIMI minor bleed. Stroke was defined as any neurological deficit that lasted more than 24 h and was confirmed by the treating physician. The diagnosis of intracranial bleed required confirmation by cerebral imaging (computed tomography or magnetic resonance imaging).

Statistical analysis

Categorical variables were presented as proportions, and continuous variables as means and SDs. Categorical variables were compared by χ^2 two-tailed testing, and continuous variables by Student's two-tailed testing for variables with normal distributions and Mann-Whitney

Figure 1) Selection of patients into the study. AMI Acute myocardial infarction; PCI Percutaneous coronary intervention; UFH Unfractionated heparin

nonparametric testing for variables with non-normal distributions. $P < 0.05$ was considered to be significant. Multivariate logistic regression analyses were performed using backward Wald regression. Covariates entered into the models for death, reinfarction and composite effectiveness end points were age, sex, diabetes, previous coronary artery disease, baseline creatinine level, fibrinolytic type, TIMI risk score, TIMI risk index, glycoprotein inhibition, type of hospital (medium/large or small; and urban or rural) and in-hospital coronary intervention. Covariates entered into the models for major bleed, stroke and composite safety end point were age, sex, previous coronary artery disease, baseline creatinine level, fibrinolytic type, glycoprotein inhibition, use of oral anticoagulant on admission, in-hospital coronary intervention and type of vascular access used for coronary intervention. All of the above covariables were entered into the final model of the primary end point of MACCE. All analyses were completed with SPSS 15.0 (SPSS Inc, USA).

RESULTS

There were 1655 patients enrolled in the AMI-QUEBEC registry. Six hundred fifty patients received fibrinolytic therapy, 843 underwent primary percutaneous coronary intervention and 162 patients did not receive any reperfusion therapy. Data concerning the type of anticoagulation were available for 600 STEMI patients who received fibrinolytic therapy. ENOX was the only LMWH used in the present study and was administered at 1 mg/kg twice daily. One hundred two patients were excluded due to missing in-hospital survival data (patients were transferred to hospitals that did not participate in the AMI-QUEBEC study). Patients with missing data on survival were younger with a lower mean heart rate, TIMI risk score and TIMI risk index on admission (Table 1). The final analysis included 498 patients – 114 patients received ENOX and 384 patients received UFH. The patient selection process is shown in Figure 1.

The baseline clinical characteristics were similar between both groups of patients (Table 2). A higher proportion of patients who received ENOX presented to medium/large hospitals. Conversely, more patients who received UFH presented to hospitals located in rural and small towns. Patients who received ENOX had more in-hospital coronary angiograms with or without interventions than patients who received UFH (61% versus 48%, $P = 0.02$). Both groups had a similar duration of delay between presentation to hospital and coronary angiogram with or without intervention (2.8 days versus 2.7 days, respectively).

Multivariate logistic regression showed that the only determinant of ENOX use was tenecteplase (TNK) (Table 3). There was no other patient- or hospital-related characteristic independently associated with the use of ENOX. Information concerning the type of fibrinolytic agent was available for all patients who received ENOX and for most patients who received UFH (Table 4). Most patients received a fibrin-specific agent – TNK was administered in 96% of patients who received ENOX. Patients in the UFH group received a variety of

TABLE 2
Baseline characteristics

Characteristics	ENOX (n=114)	UFH (n=384)	P
Age, years, mean ± SD	60.6±13	60.3±12	0.68
Female sex, %	33.3	26.6	0.16
Weight, kg, mean ± SD	78.9±19	77.5±15	0.49
Baseline creatinine level, mmol/L, mean ± SD	90.4±17	99.2±64	0.11
Mean creatinine clearance*, mL/min	88.5	87.3	0.90
Diabetes, %	12.3	12.2	0.99
Previous percutaneous coronary intervention, %	5.3	9.1	0.13
Previous cerebrovascular disease, %	3.9	5.4	0.25
Previous myocardial infarction, %	8.8	12.2	0.26
Previous CABG surgery, %	1.8	2.9	0.51
Acetylsalicylic acid use on admission, %	18.4	25.8	0.07
Oral anticoagulant use on admission, %	1.6	1.3	0.99
Clopidogrel use on admission, %	3.6	3.5	0.79
Heart rate at presentation, beats/min, mean ± SD	76±22	75±18	0.22
Systolic blood pressure at presentation, mmHg, mean ± SD	141±33	133±31	0.18
Cardiogenic shock, %	4.4	2.6	0.60
Killip class, mean ± SD	1.20±0.68	1.23±0.63	0.56
TIMI risk index, mean ± SD	25.6±9	24.8±12	0.57
TIMI risk score, mean ± SD	2.2±0.4	2.6±0.3	0.60
Clopidogrel loading, %	21.1	18.9	0.61
In-hospital glycoprotein inhibition, %	19.3	16.7	0.51
Abciximab administration, %	7.0	7.3	0.52
Medium/large hospitals (≥300 beds), %	82.2	62.2	<0.001
Rural and small town hospitals†, %	17.8	38.3	<0.001
In-hospital coronary angiogram with or without intervention, %	60.5	48.4	0.02
Delay between presentation to hospital and coronary angiogram with or without intervention, days, mean ± SD	2.8±3.2	2.7±3.3	0.90
Radial approach for coronary angiogram with or without intervention, %	63.8	50.0	0.07

*Thrombolysis in Myocardial Infarction (TIMI) risk index: heart rate × (age/10)²/systolic blood pressure. *Cockcroft-gault's method: Creatinine clearance (mL/min) = (140 – age in years) × actual weight (kg)/serum creatinine level (μmol/L) (multiply the result by 1.2 for men); †Rural and small town: population living in towns and municipalities outside the commuting zone of larger urban centres (28). CABG Coronary artery bypass graft; ENOX Enoxaparin; UFH Unfractionated heparin*

fibrinolytic drugs – bolus fibrin-specific agents were administered in 81% of patients (65% TNK and 16% reteplase).

Eleven per cent of patients who received ENOX had an in-hospital MACCE compared with 14.0% of patients who received UFH (P=0.51) (Table 5). The primary composite effectiveness end point of in-hospital death or nonfatal reinfarction occurred in 8% of the ENOX patients compared with 10% of the UFH patients. Although lower in-hospital mortality among the ENOX patients was noted compared with the UFH patients (3.5% versus 6.5% for the whole AMI-QUEBEC cohort and 3.7% versus 5.6% for the patients who received TNK), these differences were not significant. In the patients who underwent in-hospital coronary angiogram with or without intervention, no deaths occurred among the patients who received ENOX compared with 6.3% among those who received UFH (P=0.03).

Stratified analyses of bleeding complications and stroke associated with ENOX and UFH are shown in Table 6. The rate of stroke was 1.8% in patients who received ENOX and 2.9% in patients who received

TABLE 3
Determinants of enoxaparin use

	OR	95% CI	P
Age	1.01	0.98–1.04	0.68
Female sex	1.59	0.97–2.63	0.07
Weight	1.01	0.99–1.03	0.18
Killip class	0.76	0.52–1.14	0.77
TIMI risk index	1.00	0.97–1.04	0.97
Baseline creatinine level	0.99	0.98–1.00	0.19
Streptokinase	0.55	0.06–5.23	0.60
Tenecteplase	11.35	4.49–28.72	<0.001
Hospitals located in small towns and rural communities*	NA	NA	NA
Medium-size hospitals	NA	NA	NA
University teaching hospitals	NA	NA	NA
Hospitals with on-site PCI facilities	NA	NA	NA

*Thrombolysis in Myocardial Infarction (TIMI) risk index: heart rate × (age/10)²/systolic blood pressure. *Rural and small town: population living in towns and municipalities outside the commuting zone of larger urban centres (28). NA No significant association with the use of enoxaparin (OR<0.001 and P>0.99); PCI Percutaneous coronary intervention*

TABLE 4
Types of fibrinolytic therapies

Therapy	ENOX (n=114)	UFH (n=384)	P
Streptokinase	0.9	6.8	<0.001
Reteplase	0.9	16.4	<0.001
Alteplase	2.6	9.9	0.01
Tenecteplase	95.6	65.3	<0.001
Unknown	0	1.6	0.01

Data presented as %. ENOX Enoxaparin; UFH Unfractionated heparin

UFH (P=0.51). There were five confirmed intracranial bleeds, all occurring in patients who received UFH and who were 65 years of age or older; none occurred in patients who received ENOX. The multivariate logistic regressions did not show any conclusive association of ENOX with the end points of interest (Table 7).

DISCUSSION

Previous randomized trials and meta-analyses (4-13) have demonstrated the superior efficacy of ENOX compared with UFH following fibrinolytic therapy. However, the external validity of these studies (14-17) was limited by their selective inclusions of younger and less sick patients. Steinberg et al (17) showed that patients in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25) registry were older, at increased mortality risk, and had higher TIMI risk scores and Killip classes than patients enrolled in the ExTRACT-TIMI 25 trial. The safety and effectiveness of ENOX might be better evaluated in the real-life context by observational studies. Observational studies are particularly pertinent when examining the rate of bleeding complications in patients at increased bleeding risk who are generally under-represented or excluded from RCTs such as the elderly and patients on oral anticoagulants.

ENOX was associated with increased major bleeds in previous RCTs (4,20-22). ENOX was associated with a 50% increase in risk of major bleeds in the ExTRACT-TIMI 25 study (4). A total of 6.7% of patients randomly assigned to ENOX following prehospital fibrinolytic therapy had intracranial bleeds compared with 0.8% of patients randomly assigned to UFH in the Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3) PLUS study (21). Two previous observational studies (23,24) compared ENOX with the use of UFH following fibrinolytic therapy. Zeymer et al (23) reported a reduction of

TABLE 5
Stratified comparisons of the effectiveness of enoxaparin (ENOX) versus unfractionated heparin (UFH)

All patients	ENOX (n=114)	UFH (n=384)	P
Major adverse cardiac or cerebral event	13 (11.4)	54 (14.0)	0.51
Composite end point of death or nonfatal reinfarction	9 (7.9)	38 (9.9)	0.52
Death	4 (3.5)	25 (6.5)	0.10
Nonfatal reinfarction	5 (4.4)	14 (3.6)	0.88
All patients who received TNK	ENOX (n=109)	UFH (n=251)	P
Major adverse cardiac or cerebral event	13 (11.9)	28 (11.1)	0.81
Composite end point of death or nonfatal reinfarction	9 (8.3)	25 (9.9)	0.63
Death	4 (3.7)	14 (5.6)	0.38
Nonfatal reinfarction	3 (2.8)	9 (3.6)	0.88
In-hospital coronary angiogram with or without coronary intervention	ENOX (n=69)	UFH (n=191)	P
Major adverse cardiac or cerebral event	8 (11.6)	28 (14.7)	0.53
Composite end point of death or nonfatal reinfarction	4 (5.8)	20 (10.5)	0.25
Death	0 (0)	12 (6.3)	0.03
Nonfatal reinfarction	3 (4.3)	7 (3.7)	0.42
On clopidogrel before coronary angiogram with or without coronary intervention	ENOX (n=40)	UFH (n=127)	P
Major adverse cardiac or cerebral event	6 (15)	16 (12.5)	0.90
Composite end point of death or nonfatal reinfarction	2 (5.0)	10 (7.9)	0.79
Death	0 (0)	4 (3.1)	0.59
Nonfatal reinfarction	2 (5.0)	6 (4.7)	0.94

Data presented as n (%). Primary end point of major adverse cardiac or cerebral event was a composite of all-cause mortality or nonfatal reinfarction, nonfatal stroke or nonfatal major bleeding complication (intracranial bleed, and major bleeding excluding intracranial bleed or transfusion). TNK Tenecteplase

death and nonfatal reinfarction with ENOX without an increase in major bleeds in 2021 STEMI patients who received fibrinolytic therapy in the Acute Coronary Syndromes (ACOS) registry. Tatu-Chitoiu et al (24) reported similar in-hospital deaths and bleeding complications with the use of ENOX and UFH in 369 patients who received accelerated 20 min streptokinase infusion.

The meta-analyses by Mehta et al (25) and Eikelbloom et al (26) showed a 25% odds increase in intracranial bleed associated with bolus fibrinolytic agents. Risks of major and intracranial bleeds may even be higher in 'real-life' patients than in patients enrolled in the above trials due to all of the reasons mentioned above. Thus, it is particularly important to evaluate the safety profile of fibrinolytic agents, especially the risk of intracranial bleed with the combination of ENOX and TNK in unselected STEMI patients.

Zeymer et al (23) did not specify the types of fibrinolytic therapy used in the ACOS registry. Therefore, the safety and effectiveness of ENOX have not yet been adequately evaluated in unselected STEMI patients who received TNK. The effectiveness of ENOX in our study was consistent with the results of previous randomized and observational studies (4-10,23,24).

However, in contrast to previous RCTs (4,20,21), the rates of major bleeds were similar between ENOX and UFH in our unselected STEMI patients following fibrinolytic therapy. It was possible that the administration of UFH in our study was less rigorously controlled than in the previous RCTs with standardized anticoagulation protocols (4,20,21). This may have resulted in the trend toward increased bleedings in our patients who received UFH.

TABLE 6
Stratified comparisons of bleeding complications and stroke

All patients with a bleeding complication	ENOX (n=114)	UFH (n=384)	P
Composite safety end point	7 (6.1)	29 (7.5)	0.64
Stroke	2 (1.8)	11 (2.9)	0.51
Intracranial bleed	0 (0)	5 (1.3)	0.58
TIMI major bleed (excl intracranial bleed)	5 (4.4)	23 (6.0)	0.51
TIMI minor bleed	12 (10.5)	44 (11.5)	0.68
Transfusion	4 (3.5)	14 (3.6)	0.95
All patients who received tenecteplase with a bleeding complication	ENOX (n=109)	UFH (n=251)	P
Primary safety end point	7 (6.4)	13 (5.1)	0.62
Stroke	2 (1.8)	8 (3.2)	0.08
Intracranial bleed	0 (0)	4 (1.6)	0.19
TIMI major bleed (excl intracranial bleed)	5 (4.6)	8 (3.2)	0.50
TIMI minor bleed	9 (8.3)	24 (9.5)	0.36
Transfusion	4 (3.7)	5 (2.0)	0.34
Elderly patients (≥65 years of age) with a bleeding complication	ENOX (n=40)	UFH (n=136)	P
Primary safety end point	2 (5.0)	14 (10.3)	0.31
Stroke	0 (0)	6 (4.4)	0.14
Intracranial bleed	0 (0)	5 (3.7)	0.22
TIMI major bleed (excl intracranial bleed)	2 (5.0)	12 (8.8)	0.43
TIMI minor bleed	3 (7.5)	15 (11.0)	0.32
Transfusion	1 (2.5)	8 (5.9)	0.40
No in-hospital coronary intervention with a bleeding complication	ENOX (n=45)	UFH (n=201)	P
Primary safety end point	1 (2.2)	14 (6.9)	0.76
Stroke	1 (2.2)	5 (2.5)	0.92
Intracranial bleed	0 (0)	2 (1.0)	0.30
TIMI major bleed (excl intracranial bleed)	0 (0)	7 (3.5)	0.77
TIMI minor bleed	2 (4.4)	16 (8.0)	0.21
Transfusion	0 (0)	2 (1.0)	0.50
Early coronary angiogram with or without coronary intervention (≤24 h from presentation) with a bleeding complication	ENOX (n=32)	UFH (n=100)	P
Primary safety end point	5 (15.6)	17 (17)	0.92
Stroke	0 (0)	5 (5.0)	0.15
Intracranial bleed	0 (0)	2 (2.0)	0.43
TIMI major bleed (excl intracranial bleed)	5 (15.6)	15 (15.0)	0.90
TIMI minor bleed	7 (21.9)	27 (27.0)	0.18
Transfusion	4 (12.5)	11 (11.0)	0.79
Patients who received glycoprotein inhibitors with a bleeding complication	ENOX (n=39)	UFH (n=101)	P
Primary safety end point	4 (10.3)	10 (9.9)	0.95
Stroke	0 (0)	1 (1.0)	0.53
Intracranial bleed	0 (0)	0 (0)	0.99
TIMI major bleed (excl intracranial bleed)	4 (10.3)	9 (8.9)	0.81
TIMI minor bleed	6 (15.4)	11 (10.9)	0.47
Transfusion	4 (10.3)	7 (6.9)	0.51

Data presented as n (%). Primary safety end point for one of the following events: intracranial bleed, Thrombolysis in Myocardial Infarction (TIMI) major bleed or transfusion of red blood cells. ENOX Enoxaparin; excl Excluding; UFH Unfractionated heparin

It is also possible that the low rates of major bleeding complications in our patients who received ENOX were due to a shorter duration of administration (that was left to the physicians' discretion in the present study) compared with the required in-hospital duration in the previous RCTs (4,20,21). Nevertheless, because the median duration

of delay between presentation to hospital and coronary angiogram with or without intervention was 2.8 days in the ENOX patients, it is conceivable that these patients received at least 48 h of ENOX before the coronary angiogram with or without intervention. Furthermore, 24 patients (21%) received the first dose subcutaneously instead of intravenously. Subcutaneous ENOX injection may have contributed to the lower bleeding rates. Finally, the crossover rate was low, with only four patients (3.5%) whose anticoagulation was switched from ENOX to UFH. Increased major bleeding has been associated with a change of anticoagulation in the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) study (27). This low crossover rate may have contributed to the low rates of bleeding complications in our cohort.

It is of note that the use of ENOX in this registry predated its official approval as adjuvant therapy following fibrinolysis in Quebec and the recommended reduced ENOX doses for elderly patients and patients with renal failure. It is highly likely that ENOX doses were not adjusted for elderly patients and patients with renal failure in the AMI-QUEBEC cohort. Despite this, we did not observe increased major bleeds in these patients. Overall, the results of our study bring some reassuring insights into the safety and effectiveness of the combination of ENOX and TNK in 'real-life' patients.

Limitations

First, due to the observational nature of the present study, potential selection biases may have favoured the outcomes of one particular type of anticoagulant. Nevertheless, the lack of significant differences in baseline characteristics suggested that there was no major selection bias that may have invalidated the results of the study. Second, there were potential confounding biases due to differences in types of hospital and types of fibrinolytic therapy between the ENOX and UFH patients. However, the lack of independent association between the type of hospital and fibrinolytic therapy with MACCE and other effectiveness end points precluded the significant impact of these differences on the results. Third, the small sample size of the present study reduced its statistical power. The lack of differences in outcomes between the two groups of patients may be due to type II error (lack of power). Fourth, we could not include 102 patients with missing survival data. However, because these patients were young with low risk scores, adverse outcomes would be rare in these patients. Therefore, it is unlikely that inclusion of these patients would have had a major impact on our results. Finally, lack of data on duration and doses of anticoagulation limited the interpretation of our results.

CONCLUSION

In a cohort of unselected STEMI patients, there were similar rates of adverse outcomes with ENOX and UFH following fibrinolytic therapy.

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TABLE 7

Adjusted associations of enoxaparin with in-hospital major adverse events

End points	OR	95% CI	P
Major adverse end point	0.84	0.40–1.75	0.64
Composite effectiveness end point	1.01	0.43–2.40	0.98
Death	0.93	0.27–3.19	0.91
Nonfatal reinfarction	1.30	0.44–3.87	0.64
Stroke	0.84	0.16–4.48	0.84
Composite safety end point	0.71	0.25–2.03	0.52

Major adverse end point: composite end point of death, nonfatal reinfarction, nonfatal stroke or any other nonfatal major bleeding complication (major transfusion, intracranial bleed or transfusion). Composite effectiveness end point: death or nonfatal reinfarction. Composite safety end point: intracranial bleed, or major Thrombolysis in Myocardial Infarction bleed (excluding intracranial bleed) or required transfusion

The lack of significant difference in major bleeds, including intracranial bleeds, was noteworthy in view of the high proportions of patients who underwent early coronary intervention and the high use of bolus fibrinolytic agents, thienopyridines and glycoprotein IIb/IIIa inhibition. Larger observational studies may further confirm the safety, effectiveness and optimal duration of ENOX administration following bolus fibrin-specific fibrinolytic therapy in unselected STEMI patients.

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