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

Malak El-Rayes MD[1], Erick Schampaert MD[2], Jean-Claude Tardif MD[3], Mark J Eisenberg MD MPH[4], Marc Afilalo MD[4], Simon Kouz MD[5], Claude Lauzon MD[6], Richard Harvey MD[7], Michel Nguyen MD[7], Remi Kouz MD[8], Jean-Pierre Dery MD[9], Samer Mansour MD[10], Anne-Marie Van Kieu BSc[8], Stephane Rinfret MD SM[9], Thao Huynh MD MSC[11]

M El-Rayes, E Schampaert, J-C Tardif, et al. Safety and effectiveness of enoxaparin following fibrinolytic therapy: Results of the Acute Myocardial Infarction (AMI)-QUEBEC registry. Can J Cardiol 2010;26(8):431-436.

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*

L'innocuité et l'efficacité de l'enoxaparine 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'enoxaparine (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.

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.

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.

[1]*Department of Medicine, McGill University Health Centre;* [2]*Hôpital du Sacré-Coeur, Université de Montréal;* [3]*Montreal Heart Institute;* [4]*Jewish General Hospital, Montreal;* [5]*Centre hospitalier régional de Lanaudière, Saint-Charles-Borromee;* [6]*Centre Hospitalier de Thetford Mines, Thetford Mines;* [7]*Centre hospitalier universitaire de Sherbrooke, Sherbrooke;* [8]*Université de Montréal, Montreal;* [9]*Quebec Heart and Lung Institute, Quebec City;* [10]*Centre hospitalier Universitaire de l'Université de Montréal, Montreal;* [11]*McGill University Health Centre, Montreal, Quebec*

Correspondence and reprints: Dr Thao Huynh, Department of Medicine, McGill University, 1650 avenue Cedar, Montreal, Quebec H3G 1A4.

Telephone 514-934-1934 ext 43241, fax 514-934-8569, e-mail thao.huynhthanh@mail.mcgill.ca

Received for publication October 13, 2008. Accepted March 22, 2009

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

Characteristics	Data on survival status: Available (n=498)	Missing (n=102)	P
Age, years, mean ± SD	60.3±12	54.6±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 ± SD	74±20	69±13	0.04
Systolic blood pressure at presentation, mmHg, mean ± SD	138±31	130±24	0.09
Killip class, mean ± SD	1.23±0.65	1.07±0.26	0.17
TIMI risk index, mean ± SD	21.3±9	17.1±11	0.009
TIMI risk score, mean ± SD	2.12±2.4	1.07±1.9	0.01

Thrombolysis in Myocardial Infarction (TIMI) risk index: heart rate × [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

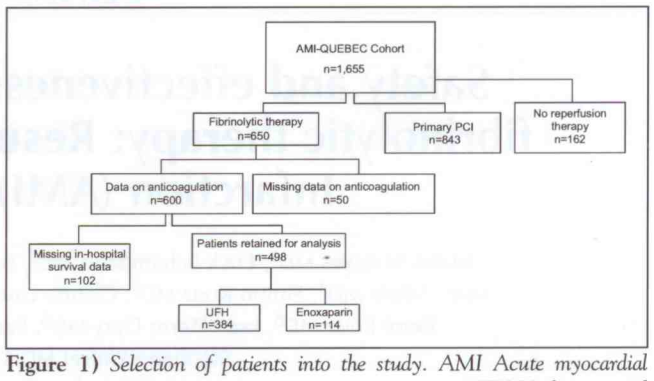

Figure 1) *Selection of patients into the study. AMI Acute myocardial infarction; PCI Percutaneous coronary intervention; UFH Unfractionated heparin*

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