The delay to thrombolysis: an analysis of hospital and patient characteristics

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Abstract

Objective: To describe the various components of the delay to thrombolytic treatment for patients with acute myocardial infarction (MI) and to identify the hospital and patient characteristics related to these delays.

Design: Cohort analysis from a hospital registry of patients receiving thrombolytic treatment.

Setting: Forty acute care hospitals in Quebec.

Subjects: All 1357 patients who received thrombolysis between January 1995 and May 1996.

Main outcome measures: Time from onset of symptoms to arrival at hospital and the various components of the in-hospital delay.

Results: The median delay before presentation to hospital was 98 (interquartile range [IR] 56 to 180) minutes and was longer for women ($p < 0.001$), patients over 65 years of age ($p < 0.001$) and patients with diabetes mellitus ($p < 0.01$). The median time from arrival at hospital to thrombolysis was 59 (IR 41 to 89) minutes, the medical decision-making component taking a median of 12 (IR 4 to 27) minutes. Women ($p < 0.05$), older patients ($p < 0.001$) and patients with a past history of MI ($p < 0.001$) had increased in-hospital delays to thrombolysis. Delays were longer in community hospitals ($p < 0.05$) and low-volume centres ($p < 0.01$) and when a cardiologist made the decision to administer thrombolysis ($p < 0.001$). Multivariate analysis showed that increased age (odds ratio 1.5, 95% confidence interval 1.3 to 1.7, $p < 0.001$) and having the medical decision made by a cardiologist (odds ratio 1.8, 95% confidence interval 1.6 to 2.0, $p < 0.001$) were independently associated with an increased risk of being in the upper median of in-hospital delays.

Conclusions: Despite certain improvements, there remain substantial delays between symptom onset and the administration of thrombolysis for patients with acute MI. A large part of the delay is due to the hesitation of patients (particularly women, older patients and patients with diabetes) to seek medical attention. Although the median time for medical decision-making appears reasonable, care must be taken to ensure that all patient groups receive timely evaluation and therapy. The delay associated with having the treatment decision made by a cardiologist probably represents a marker for more difficult, complex cases. Methods should be developed to permit specialty consultation, if needed, while minimizing treatment delays. Community and low-volume hospitals may require special attention.

Résumé

Objectif : Décrire les divers éléments du retard du traitement thrombolytique chez les patients victimes d'un infarctus aigu du myocarde (IM) et définir les caractéristiques de l'hôpital et des patients qui ont trait à ces retards.

Conception : Analyse par cohortes tirées du registre des patients qui ont reçu un traitement thrombolytique dans un hôpital.

Contexte : Quarante hôpitaux de soins actifs au Québec.

Sujets : Les 1357 patients qui ont reçu un traitement thrombolytique entre janvier 1995 et mai 1996.

Principales mesures de résultats : Temps écoulé entre l'apparition des symp-

Evidence

Études

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tômes et l'arrivée à l'hôpital et les divers éléments du retard survenu à l'hôpital.

Résultats : Le temps médian écoulé avant l'arrivée à l'hôpital s'est établi à 98 (intervalle interquartile [II] de 56 à 180) minutes et a été plus long dans le cas des femmes ($p < 0,001$), des patients de plus de 65 ans ($p < 0,001$) et des patients atteints de diabète sucré ($p < 0,01$). La durée médiane de la période écoulée entre l'arrivée à l'hôpital et l'administration du traitement thrombolytique s'est établie à 59 (II de 41 à 89) minutes; le volet de la prise de décision médicale a pris en moyenne 12 (II de 4 à 27) minutes. Le temps écoulé à l'hôpital avant l'administration du traitement thrombolytique a été plus long dans le cas des femmes ($p < 0,05$), des patients âgés ($p < 0,001$) et des patients qui avaient déjà subi un IM ($p < 0,001$). Les retards ont été plus longs dans les hôpitaux communautaires ($p < 0,05$) et les centres à faibles volumes ($p < 0,01$) et lorsqu'un le cardiologue a décidé d'administrer le traitement thrombolytique ($p < 0,001$). Une analyse à variables multiples a démontré un lien entre l'âge plus avancé (rapport des cotes de 1,5, intervalle de confiance à 95 % de 1,3 à 1,7, $p < 0,001$) et un risque accru pour une personne de se retrouver dans la médiane supérieure des retards survenus à l'hôpital, et entre la prise de la décision médicale par un cardiologue (rapport des cotes de 1,8, intervalle de confiance à 95 % de 1,6 à 2,0, $p < 0,001$) et un tel risque.

Conclusions : En dépit de certaines améliorations, il persiste encore des retards importants entre l'apparition des symptômes et l'administration de la thérapie thrombolytique aux patients victimes d'un infarctus aigu du myocarde. Une partie importante du retard est attribuable au fait que les patients (en particulier les femmes, les patients âgés et les personnes diabétiques) hésitent à consulter un médecin. Même si le temps médian nécessaire à la prise de décisions médicales semble raisonnable, il faut veiller à ce que tous les groupes de patients soient évalués et traités rapidement. Le retard associé au fait que la décision relative au traitement a été prise par un cardiologue représente probablement un indicateur de cas plus difficiles et complexes. Il faudrait mettre au point des façons de permettre la consultation de spécialistes au besoin tout en réduisant au minimum les retards du traitement. Il faudra peut-être accorder une attention spéciale aux hôpitaux communautaires et aux établissements à faibles volumes.

Large clinical trials have definitively shown the value of thrombolysis in acute myocardial infarction (MI).[1–3] Furthermore, these and other trials have shown that the benefit of this therapy can be maximized with earlier treatment.[4,5] However, for unclear reasons, the literature suggests that this therapy has not fully permeated clinical practice.[6] Moreover, important delays in the administration of this treatment have been observed.[7,8] These delays may reduce the efficacy of thrombolysis by increasing not only mortality[9] but also morbidity.[10] In an attempt to rectify this situation, clinical guidelines have been published to assist in the identification of appropriate patients for treatment.[11] These guidelines include a benchmark for delays in drug administration of 60 minutes, and recently 30 minutes has been advanced as the standard.[12]

To address these concerns, the Fonds de recherche en santé du Québec established the Quebec Acute Coronary Care Working Group within a cardiovascular network whose goal is to reduce coronary morbidity and mortality by 25% before the next millenium. In addition to stimulating collaborative research, another goal of the group has been to evaluate the performance of both university-affiliated and community hospitals in the use of thrombolytic agents and to provide feedback to the participating centres. In this report we present the initial findings of a province-wide registry of patients admitted for acute coronary syndromes. We describe the various components of the delay to thrombolytic treatment in routine practice over a large spectrum of Quebec hospitals and identify the hospital and patient characteristics related to these delays.

Methods

Data acquisition

Forty-four (52%) of the 85 Quebec acute care hospitals approached agreed initially to participate in this voluntary registry. Subsequently 4 hospitals, contributing fewer than 10 patients each, elected not to participate and were excluded from further analysis. There were no obvious differences between the participating and nonpartici-

pating institutions. Fourteen of the 16 major Quebec health districts had hospital participation. The hospitals represented a cross-section of urban (15 hospitals), rural (25), tertiary (9) and community (31) institutions. Each hospital contributed data for 1 year, and data collection occurred from January 1995 to May 1996.

Each patient admitted to a participating hospital with a presumptive diagnosis of an acute ischemic syndrome was entered prospectively into the registry. On admission, this involved the completion of a one-page questionnaire containing patient demographic and clinical information, including the risk profile, electrocardiographic (ECG) data, and information on the administration of thrombolytic agents and on any complications. The time of onset of symptoms, of arrival at hospital, of diagnostic ECG, of the medical decision to proceed with thrombolysis and of the start of therapy were also recorded. The time of arrival refers to patient registration before any diagnostic testing or medical consultation. It was therefore possible to clearly separate the delay in receiving thrombolysis into prehospital and in-hospital components.

At hospital discharge a systematic chart review was performed to establish the resources used and final diagnosis. Specially trained and designated nurse coordinators collected the data at each centre. The data were sent to the coordinating centre and, after validation, were entered twice in the computer, the program software verifying their consistency. Local approval was obtained to collect these anonymous data in compliance with local ethics guidelines.

Data analysis

We examined in detail the components of delay in administering thrombolysis, separating in-hospital (door-to-needle) delays into the time to obtain the diagnostic ECG, the time to make the medical decision and the time to prepare the drug. Since these time distributions were heavily skewed, medians and interquartile ranges (IRs) are reported. We performed a univariate analysis between the various components of the delays and patient and hospital characteristics using nonparametric statistical tests (Wilcoxon rank-sum test). Statistically significant variables ($p < 0.10$) from this univariate analysis were included in a multivariate logistic regression model (based on time greater or less than the median in-hospital delay) to determine the independent predictors of delay in treatment. All statistical analyses were performed with the use of SAS software (version 6.11, Cary, NC).

Results

During the study period data were collected for 8917 patients admitted with a suspected acute ischemic syndrome. A final diagnosis of acute MI was made in 3741 patients, of whom 1357 (36.3%) received thrombolytic therapy in 40 different hospitals.

The patient characteristics are presented in Table 1. The average age was 60.2 years. Streptokinase was used in 925 cases (68.2%) and tissue plasminogen activator (tPA) in 432 (31.8%). One-fifth of the patients had a past history of MI. As expected, the prevalence of the conventional risk factors was high.

The median time from the onset of symptoms to arrival at the emergency department was 98 (IR 56 to 180) minutes, and the median time from hospital arrival to thrombolysis was 59 (IR 41 to 89) minutes (Table 1). Substantial delays occurred at all phases of the in-hospital process. Unfortunately, various intervals were missing for 15% of the patients. Furthermore, the site of thrombolysis (emergency department v. coronary care unit) was not systematically recorded.

Table 2 shows the effect of hospital characteristics on the door-to-needle time and its various components. Tertiary centres performed slightly better than community centres at each phase of the process, although the only statistically significant difference was in the median time from arrival at the emergency department to the diagnostic ECG (12 minutes v. 15 minutes) ($p < 0.05$), leading to a 3-minute de-

Table 1: Characteristics of 1357 patients who received thrombolysis at 1 of 40 acute care hospitals in Quebec between January 1995 and May 1996*

Characteristic	Value
Sex, % (and no.) of patients	
Male	73.7 (997/1353)
Female	26.3 (356/1353)
Mean age (and standard deviation), yr	60.2 (12.3)
% (and no.) of patients	
With past history of MI	21.3 (273/1282)
Current smokers	55.4 (667/1204)
With diabetes mellitus	14.7 (188/1279)
With high blood pressure	30.1 (389/1292)
With dyslipidemia	32.6 (405/1242)
With anterior MI	38.0 (502/1321)
Thrombolytic agent received, % (and no.) of patients	
Streptokinase	68.2 (925/1357)
Tissue plasminogen activator	31.8 (432/1357)
Median time (and IR), min	
From onset of symptoms to arrival at ED	98 (56–180)
From arrival at ED to diagnostic ECG	15 (8–28)
From diagnostic ECG to decision to administer thrombolytic	12 (4–27)
From decision to administer thrombolytic to drug administration	22 (15–34)
Total, from hospital arrival to thrombolysis	59 (41–89)
Total, from onset of symptoms to thrombolysis	172 (115–270)

Note: MI = myocardial infarction, IR = interquartile range, ED = emergency department, ECG = electrocardiogram.
*Excluding missing responses.

crease in door-to-needle time. If the decision to administer thrombolysis was made by a cardiologist, the time from arrival at the emergency department to the diagnostic ECG, the time from the diagnostic ECG to the decision to administer thrombolysis and the door-to-needle time were increased by 3, 5 and 13 minutes ($p < 0.001$) respectively.

Low-volume centres were defined a priori as hospitals whose volume was in the lowest quartile of the distribution of patients who received thrombolysis per centre. This cut-off point was 23 patients treated per centre per year. Nineteen centres treating a total of 143 patients were thus identified as low-volume centres. These centres had marginally slower performance at each stage of the process than the high-volume centres, and the door-to-needle time was 11 minutes longer ($p < 0.01$).

The patient characteristics associated with delayed pres-entation and longer in-hospital time to treatment are shown in Table 3. Women and older patients presented significantly later after symptom onset than men and younger patients respectively ($p < 0.001$). Patients with diabetes mellitus presented later than those without diabetes (119 minutes v. 95 minutes) ($p < 0.01$) but experienced no in-hospital delays (data not shown). However, medical decision-making was longer for women, older patients and patients with a past history of MI, with median delays of 6, 4 and 3 minutes ($p < 0.05$) respectively, prolonging the door-to-needle time by 8 ($p < 0.05$), 10 ($p < 0.001$) and 9 ($p < 0.001$) minutes respectively. Neither the choice of thrombolytic agent nor the infarct location (anterior v. inferior) influenced any of the delay components.

A multivariate logistic regression model showed that increased age (odds ratio 1.5, 95% confidence interval 1.3 to 1.7, $p < 0.001$) and having the medical decision made by a cardiologist (odds ratio 1.8, 95% confidence interval 1.6 to 2.0, $p < 0.001$) were independently associated with an increased risk of being in the upper median of in-hospital delays.

Discussion

Our study is the first to describe the detailed components of the delay to thrombolytic treatment in routine practice over a large spectrum of Quebec hospitals. In addition, the hospital and patient characteristics related to these delays have been identified. The data were collected prospectively and reflect recent practice patterns. By including the full spectrum of patients presenting with acute MI, the registry mirrors the "real world" more comprehensively than clinical trials, which are often limited to specific subgroups of patients.

We noted significant delays at all the various stages of the treatment process. The most important delay in instituting treatment was the reluctance of patients to present promptly to the emergency department when they experienced characteristic cardiac symptoms. Even patients with previous infarctions, who should have received the conventional advice to present rapidly if such symptoms occur, delayed consultation. In particular, women and older people seemed to endure symptoms longer. The greater delay in seeking treatment noted for people with diabetes has not been highlighted previously and suggests that diabetic sensory neuropathy causing symptom attenuation is responsible.

Overall, 50% of our cohort received thrombolysis within 1 hour of hospital presentation. This is a significant improvement over the results of Cox and col-

Table 2: Median delays according to hospital-specific characteristics*

	Median time (and IR), min					
	Hospital affiliation		Physician status		Volume of activity	
Interval	Tertiary *n = 478*	Community *n = 879*	ER physician *n = 706*	Cardiologist *n = 613*	High *n = 1214*	Low *n = 143*
From onset of symptoms to arrival at ED	101 (60–180)	95 (55–180)	95 (60–180)	102 (54–180)	100 (59–180)	90 (50–180)
From arrival at ED to diagnostic ECG	12 (6–25)	15† (9–29)	13 (7–23)	16† (10–35)	14 (8–27)	15 (7–29)
From diagnostic ECG to decision to administer thrombolytic	11 (3–27)	13 (5–27)	10 (3–23)	15† (6–33)	12 (4–26)	15 (4–38)
From decision to administer thrombolytic to drug administration	20 (15–31)	23 (15–35)	22 (15–34)	22 (15–35)	22 (15–34)	25 (15–36)
Total, from hospital arrival to thrombolysis	57 (36–86)	60‡ (44–90)	53 (40–78)	66† (45–110)	58 (41–87)	69§ (48–111)
Total, from onset of symptoms to thrombolysis	164 (110–270)	175 (117–270)	158 (110–250)	180† (125–290)	170 (115–269)	187 (115–339)

*Excluding missing responses.
†$p < 0.001$.
‡$p < 0.05$.
§$p < 0.01$.

leagues,[10] who reported that 75% of patients enrolled in Canadian hospitals in the first international Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO-I) trial waited more than 1 hour before treatment. Since the GUSTO data were collected in 1991–92, it is unclear how much of this improvement is due to increased awareness of the importance of rapid treatment. The GUSTO data may have also provided inflated measures of contemporary delays by adding their own intrinsic delay related to enrolment and research protocol. Despite the improvement noted in our study, less than 25% of our cohort received thrombolysis in the ideal 30-minute period currently recommended.[12]

Our study permitted an in-depth analysis of the in-hospital components of the delay to treatment. The median time between presentation to the emergency department and the diagnostic ECG was 15 (IR 8 to 29) minutes. This suggests that triage mechanisms may be improved. The median of 22 minutes for drug preparation seems inordinately long, and efforts should be directed at greatly reducing this interval.

The medical decision-making process, which includes adequate history taking, a search for possible contraindications to thrombolysis, physical examination and interpretation of the ECG, took a median of 12 (IR 4 to 27) minutes, which seems appropriate. Although we accept that certain presentations are more difficult to assess, it is disconcerting to observe the statistically significant delays in decision-making for women, older patients and patients with a past history of MI, each being a high-risk group. In the case of women and older patients this amounts to double jeopardy, because these groups also delay in presenting to the emergency department. These longer delays may partially contribute to the known increased in-hospital mortality among women and older patients.

Decision-making that involved a cardiology consultation increased the median door-to-needle time by 13 minutes ($p < 0.001$). It would be erroneous to interpret this p value as the probability that the null hypothesis (no difference between cardiologist and emergency department physicians) is true or, equivalently, the probability of making an error in rejecting the null hypothesis.[13] Cardiologists have been shown to be more aware of clinically proven, evidence-based medical therapies, including thrombolysis, than primary care physicians and to use them more frequently.[14,15] Thus, it appears reasonable to assume that they should also be rapid decision-makers. Certainly not all patients who eventually receive thrombolysis present initially with a clear-cut indication, and the delay associated with a cardiologist decision-maker may be a marker for these more complex cases. This view is supported by the significantly longer time to acquire the diagnostic ECG when the physician was a cardiologist, which implies that earlier ECGs were perhaps ambiguous. From a Bayesian perspective, these arguments imply a very low prior probability that cardiologists would be poorer performers, and our findings are by no means strong enough to contradict this prior belief.[16]

It is therefore possible that the additional delay associated with a cardiologist decision-maker is appropriate in more complex cases. However, this cannot be proven from our data. Although the clinical significance of this supplemental delay is uncertain and perhaps well justified for difficult cases, it also sends a warning that local institutions should examine

Table 3: Median delays according to patient-specific characteristics*

	Median time (and IR), min									
	Sex				Age, yr				Past history of MI			
Interval	Male *n = 978*		Female *n = 346*		≤ 65 *n = 835*		> 65 *n = 521*		No *n = 1008*		Yes *n = 273*	
From onset of symptoms to arrival at ED	90	(51–172)	120†	(70–210)	83	(50–160)	120†	(65–200)	98	(57–180)	98	(55–192)
From arrival at ED to diagnostic ECG	14	(8–28)	15	(8–27)	14	(8–26)	15	(8–30)	15	(8–27)	15	(8–30)
From diagnostic ECG to decision to administer thrombolytic	11	(3–26)	17†	(7–30)	11	(4–25)	15†	(5–32)	12	(4–26)	15‡	(5–36)
From decision to administer thrombolytic to drug administration	22	(15–35)	25	(15–35)	22	(15–34)	23	(15–35)	22	(15–33)	22	(15–35)
Total, from hospital arrival to thrombolysis	57	(40–88)	65‡	(46–93)	55	(40–85)	65†	(47–93)	57	(40–85)	66†	(46–96)
Total, from onset of symptoms to thrombolysis	160	(110–265)	190†	(135–300)	155	(105–252)	195†	(135–311)	169	(113–260)	185‡	(128–307)

*Excluding missing responses.
†$p < 0.001$.
‡$p < 0.05$.

their performance to ensure that specialty consultation does not unnecessarily prolong door-to-needle times for routine cases. Simultaneous cardiology consultation while patient evaluation is under way is one means of permitting specialty involvement, if required, without incurring further delays.

Other institutional characteristics associated with increased delays were community hospitals and low-volume centres. The association of improved quality of care with high volume of activity has been previously noted in other domains of cardiology.[17,18]

The limitations of our study should be appreciated. Although the data for this registry were entered by trained research nurse coordinators and were validated when entered in the database, financial constraints prevented external validation of the source documents. Nevertheless, it seems reasonable to assume that the large size of the cohort (nearly 9000 patients) precluded systematic biases in data entry. The length of the data acquisition period (12 months for each centre) makes the Hawthorne effect (improved performance since centres knew they were being monitored) unlikely. Although there were no obvious systematic biases in the missing data in our study, this incompleteness limits the strength of our conclusions. Finally, our findings do not permit any conclusions about the appropriateness of thrombolysis in this cohort. Such analysis would require blinded data extraction from the medical charts and evaluation by an expert panel using accepted national treatment guidelines.

From a public health perspective, it appears that renewed efforts are needed to understand why patients delay in presenting to emergency departments when they are experiencing typical cardiac symptoms for a certain time. The importance of cognitive (correctly attributing the ischemic origin of the symptoms) and affective (higher anxiety and comfort in seeking medical care) responses in decreasing the length of delay before presentation has been recognized.[19] However, the interaction between patient demographic features and personality traits, social structures and the health care system is very complex, and more extensive research in this area is clearly required.[20] Our findings suggest that these efforts should be directed particularly at women, older people, those with diabetes and those with a past history of MI. Physicians must continue to educate their patients about the importance of seeking medical care promptly for suspected cardiac symptoms. However, they should be aware of possible barriers limiting the effectiveness of this intervention.

In general, the time for medical decision-making appears reasonable, but care must be taken to ensure that all patient groups receive timely evaluation and therapy. However, a large part of the delay in starting thrombolytic treatment arises from factors external to the medical decision-making process. Institutions with low volumes, for example, may need special attention. Physicians who treat patients with MI should assist in the organization of their emergency departments to facilitate the rapid collection of data and the preparation of thrombolytic agents. Further study is required to understand better the mechanisms of the delays identified in this study.

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