Medical Decision Making in the Choice of a Thrombolytic Agent for Acute Myocardial Infarction

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Little is known about how physicians make decisions when the evidence is incomplete or controversial. While thrombolysis improves survival following acute myocardial infarction (AMI), conflicting evidence exists as to any specific agent's superiority, particularly if cost–effectiveness is considered. Using a Bayesian hierarchical model, the authors examined the patient, physician, and hospital characteristics that are related to the decision-making process concerning the choice of thrombolytic agent in a prospective registry of 1,165 AMI patients receiving thrombolysis. Tissue plasminogen activator (t-PA) was administered to 432 patients (31.8%) and streptokinase (SK) to the remainder. The presence of an anterior infarction, a previous myocardial infarction, low blood pressure, a cardiologist decision maker, younger age, and receiving treatment within six hours after the start of symptoms were independent predictors of receiving t-PA. The levels of importance that physicians accorded to these patient characteristics differed according to their practicing institutions. Generally, they followed evidence-based medicine and reasonably targeted high-risk patients to receive the more expensive t-PA. However, they also preferentially treated younger patients, where only a small absolute advantage appears to exist. *Key words*: acute myocardial infarction; Bayesian modeling; evidence-based decision making; Gibbs sampling; hierarchical model; physician decision making; thrombolysis. **(Med Decis Making 1999;19:411–418)**

Medical decision making encompasses a variety of perspectives, from subject-level decision making based on patient-specific information and utilities to cost–effectiveness studies and the formation of clinical guidelines that suggest optimal treatment and diagnostic patterns for groups of patients. Comparatively little attention, however, has been paid to identifying the factors that influence physicians' behaviors in practice, especially in areas where the literature may be conflicting or when economics may enter into the decision making. In this study we investigated the characteristics of patients, physicians, and hospitals in relation to patterns of use of thrombolytic agents in the management of myocardial infarction (AMI).

Large clinical trials have conclusively shown the value of thrombolysis in treating AMI.[1] There have been three mega-trials comparing the two thrombolytic agents commercially available in North America.[2–4] The GISSI-2 and ISIS-3 studies found no meaningful difference between 1.5 million units of intravenous streptokinase (SK) administered over one hour and 100 mg of intravenous tissue plasminogen activator (t-PA) administered over three hours. Using a regimen of accelerated t-PA with intravenous heparin, the GUSTO investigators[4] found a statistically significant net clinical benefit (combined outcome of death or nonfatal stroke) in favor of t-PA.

The disparity in these findings has produced enormous controversy over the choice of the ''best'' agent.[5–10] While this controversy largely settles on how to reconcile the totality of evidence, it is undoubtedly fueled, at least in part, by the large price differences between the two agents. For example, in Canada t-PA costs approximately $US 1,450 more per dose than SK. Even national expert panels have recognized the difficulties in choosing a thrombolytic

Received November 4, 1998, from the Department of Medicine of Centre Hospitalier de l'Université de Montreal (CHUM) (JMB, LJ); the Department of Epidemiology and Biostatistics, McGill University (LJ); and the Division of Clinical Epidemiology and Centre for the Analysis of Cost Effective Care, Department of Medicine, Montreal General Hospital (LJ); and the Department of Medicine Institut de Cardiologie (PT); all in Montreal, Quebec, Canada. Revision accepted for publication June 2, 1999.

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agent and have on occasion presented endorsed options ranging from almost exclusive use of one agent or the other as being acceptable practice.[11] Other practice guidelines for the management of AMI patients have elected not to make specific recommendations for the choice of agent.[12] It is unknown how practicing clinicians have interpreted this conflicting clinical information about the relative effectiveness and costs of the different therapeutic agents and integrated it into their routine practice.

It is well established that physician practice patterns in cardiovascular medicine vary at both international[13–17] and national[18–21] levels. Within a given health care system, much of the variations can be explained by patient, physician, and hospital characteristics. Among AMI patients, specific patient characteristics potentially influencing resource utilization, including the choice of thrombolytic agent, are disease severity and patient demographic factors such as age and sex. Physicians' characteristics that may affect resource utilization decisions include specialty training and region of practice.[13,14,19,22,23] Finally, hospital status (university or community), location (urban or rural), and the volume of activity may influence the choice of cardiovascular care.[24,25]

Previous studies have concentrated on identifying patient groups not receiving thrombolytic therapy but have incidentally revealed large international variations in the selection of these agents.[26,27] In Europe, the ratio of SK use to t-PA use is about 7:1 (personal communication, P. Sleight, K. Woods), while in the United States the ratio is 1:3 in favor of t-PA.[28] Canada has a universal health care system, similar to those of most European countries, but also has strong medical ties to the United States, and therefore the relative use of these two agents in Canada is presumed to fall between these two extremes.

Here we report the results from an analysis of a clinical registry of AMI patients in Quebec, Canada, that was established to understand the process of care in acute coronary syndromes. This registry permitted an examination of how patient, physician, and hospital characteristics influence the choice of thrombolytic agent. To our knowledge, no other study has examined this process of medical decision making. Given the high costs of treating AMI and its complications, it is important to understand factors influencing physician choice of thrombolytic agent. This will become even more important as new agents presently being studied eventually are delivered to the marketplace.[29]

Methods

DATA ACQUISITION

Forty-four Quebec acute care hospitals, representing a broad spectrum of tertiary, community, urban, and rural institutions, agreed to participate in a clinical registry examining acute coronary syndromes. This registry was established within a cardiovascular network funded by the Fonds de la Recherche en Santé du Québec. The data were collected from January 1995 to May 1996. The details of the registry have been previously described, and no obvious difference between participating and non-participating hospitals was found.[30] Trained re-

Table 1 • Characteristics of the Thrombolytic Cohort with No Missing Values (n = 1,165)

	Streptokinase (SK) (n = 794)	Tissue Plasminogen Activator (t-PA) (n = 371)	Difference, SK − t-PA (95% CI)
Men	73.8%	74.9%	−1.1 (−6.0, 4.0)
Age, median (interquartile range)	62 years (51–70)	58 years (50–68)	4 (2.5, 5.5)
Age > 65 years	40.2%	34.2%	6.0 (0.1, 12.0)
Systolic BP on arrival, median (interquartile range)	140 mm Hg (125–160)	135 mm Hg (110–160)	5.0 (1.0, 9.0)
Anterior myocardial infarction	33.8%	50.1%	−16.3 (−10.0, −22.5)
Previous myocardial infarction	17.4%	29.4%	−12.0 (−6.6, −17.6)
Cardiologist decision maker	43.8%	52.8%	−9.0 (−2.7, −15.3)
Time from pain to thrombolysis > 6 hours	16.6%	11.1%	5.5 (1.1, 9.8)
Diabetes	16.2%	11.1%	5.1 (1.2, 9.8)
Previous use of aspirin	19.3%	25.9%	−6.6 (−1.1, −12.0)
Pprevious use of beta-blockers	12.7%	17.7%	−5.0 (−0.3, −9.7)
Previous history of hyperlipidemia	28.7%	36.8%	−8.1 (−2.1, −14.1)
Previous history of hypertension	30.5%	26.6%	3.9 (−1.8, 9.6)
Previous history of CABG‡	3.4%	4.5%	−1.1 (−3.7, 1.5)
Previous history of ACE-I§	8.3%	9.1%	−0.8 (−4.5, 2.9)
BP on arrival	23.0%	34.5%	−11.5 (−5.6, −17.3)
Tobacco use	56.6%	51.2%	5.4 (−0.1, 11.7)
Previous history of cerebrovascular accident	4.2%	3.3%	0.9 (−1.6, 3.3)

‡CABG = coronary artery bypass grafts.
§ACE-I = angiotensin-converting enzyme inhibitors.

search nurse coordinators prospectively entered all patients admitted with acute ischemic syndromes (n = 8,917) into the registry, and the 1,357 patients receiving thrombolysis formed the basis of this study. The hospitals represented a cross section of urban, rural, university, and community institutions. Local approval was obtained to collect these anonymous data.

DATA ANALYSIS

Baseline summary statistics of the demographic and clinical variables for the thrombolytic cohort as a whole were calculated. A univariate analysis comparing patient characteristics within each thrombolytic-agent group was next performed. The variables examined are listed in table 1. As a first step, potentially important variables were included in a standard multivariate logistic regression model to determine the independent predictors of the choice of thrombolytic agent.

This analysis is incomplete, however, since, in addition to patient characteristics, it is likely that hospital characteristics influence the choice of one agent over another. For example, physicians in one hospital may make their choices of which agent to use differently from physicians in another hospital. These effects were investigated through a Bayesian random-effects hierarchical model. Conceptually, the participating hospitals may be imagined to be like a random sample from a super population of all possible hospitals where AMI patients may be treated with thrombolysis. A separate logistic regression equation is created for each hospital. The ensemble of coefficients for the individual regression parameters from all hospitals is used to estimate the distribution of the effects across hospitals. If this distribution covers only a very narrow range of values, then the effect of the variable in question is similar across hospitals (as is assumed by standard logistic regression), meaning that physicians use the available information similarly across hospitals. Larger ranges imply that the effects differ from hospital to hospital. In the latter situation, it can be useful to try to explain the observed effect differences through a linear regression model using as explanatory variables hospital characteristics, including location, university affiliation, and volume of activity. At this level of the model, the unit of analysis has become the hospital rather than the patient. The hospital volume of activity was treated as a continuous variable. For stability of the estimates, we grouped the lowest-volume centers (< 10 cases) together. Therefore, for the hierarchical modeling, 26 hospitals (25 hospitals together with one ''hospital'' that was a composite of the 15 small-volume institutions) were considered. The hospitals represented 14 of 18 different health regions throughout Quebec (two of the missing regions account for only 0.3% of the total population). Since the unit of analysis at this level is the hospital, because of small numbers it was uninformative to model the effect of location using the individual regions. Consequently, hospital location was dichotomized into urban (Montreal and Quebec City) and rural (all other). University affiliation was also dichotomized into tertiary care and non–tertiary care centers. With data from over 1,000 patients but only 26 hospitals, first-level parameters are likely to be estimated with higher precision than second-level parameters.

The choice of hospital variables to include in the linear models for each patient parameter across the different hospitals was determined by approximate Bayes factors, as calculated by the Bayesian information criterion.[31] A more detailed description of our model is provided in the appendix. A comprehensive discussion of hierarchical modeling for the analysis of practice patterns is available elsewhere.[32]

Results

During the period of observation, data were collected from 8,917 patients admitted with suspected acute ischemic syndromes. AMI was the final diagnosis for 3,741 patients, of whom 1,357 received thrombolytic therapy in 40 different hospitals. SK was given to 925 patients (68.2%) and t-PA to 432. Complete information for all variables was available for 1,165 patients (85.9%). A comparison between patients with and without missing values did not reveal any systematic difference in the available data.

Of the 40 hospitals in which the patients were treated 15 were urban and 25 were rural. Nine were tertiary care hospitals and eight others had some degree of university affiliation. Urban hospitals contributed 549 (47.1%) of the patients, and 371 (33.6%) were hospitalized in tertiary care centers. Of the patients treated in urban centers, 192 (35.0%) received t-PA, compared with 179 (29.1%) in rural centers (difference = 5.9%, 95% CI = 0.3–11.4%). The patients in tertiary care institutions received t-PA more commonly than did the patients in non–tertiary care centers (43.0% vs 26.2%, difference = 16.8%, 95% CI 10.7–22.7%). Figure 1 is a plot of the percentage use of t-PA as a function of the number of cases of thrombolysis for each hospital. There was wide variation in the institutional use of t-PA but no obvious association between use of t-PA and volume of activity.

The available patient and physician characteristics are shown in table 1. Overall, 73.9% of the patients were male, with similar sex distributions in the two thrombolytic groups. Compared with SK-treated patients, those administered t-PA were younger, had

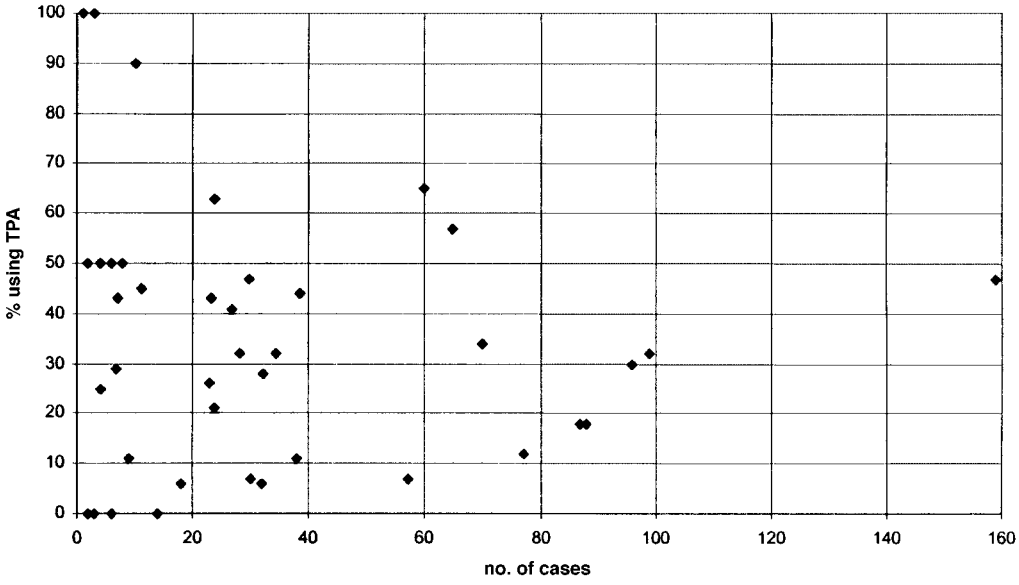

FIGURE 1. Plot of percentage uses of t-PA as a function of thrombolytic caseload for the participating hospitals.

lower systolic blood pressures on admission, were more likely to have past histories of prior myocardial infarction or an anterior infarction, and more frequently had a cardiologist make the therapeutic decision for thrombolysis. Among those receiving SK, diabetes was more common, but known hyperlipidemia and prior treatment with aspirin or beta-blockers were less prevalent. Smoking, previous history of hypertension, prior stroke or coronary artery bypass graft surgery, and use of angiotensin-converting enzyme inhibitors were approximately equally prevalent in the two groups.

The results from a standard fixed-effects logistic regression analysis of the patient characteristics predictive of the selection of a specific thrombolytic agent are presented in table 2. The odds of receiving t-PA were less for elderly patients and those initially receiving treatment beyond six hours after the start of symptoms. On the other hand, the presence of an anterior infarction, a previous myocardial infarction, and a low blood pressure were independent predictors of receiving t-PA. Finally, the involvement of a cardiologist decision maker was also an independent predictor of receiving t-PA. The presence of diabetes was not strongly associated with the choice of agent, although it is a well known predictor of adverse events following AMI. Gender, other past medical history, and previous medications were also not independently associated with the choice of therapy.

The above model, however, assumes that the impact of each characteristic is the same across all hospitals. A more realistic random-effects or hierarchical model would account not only for within-hospital but also for between-hospital variations. Results from this random-effects or hierarchical model do not substantially alter the point estimates of the above regression parameters, but the credible intervals (Bayesian analogs of standard confidence intervals) are generally wider, since both the between-hospital and the within-hospital variations are now included (see table 2). The widths of the credible intervals belonging to the cardiologist decision maker and the electrocardiographic site of the infarction increased the most, signifying the importance of the between-hospital variations for these factors.

We next examined the information collected about the participating hospitals, including volume of activity, geographic location, and university status, to see whether these characteristics could explain the between-hospital variations in the above parameter estimates. These issues were investigated by adding a linear regression component to the hierarchy (see the appendix).

Overall, the tertiary care (university) hospitals systematically had higher rates of t-PA use but without altering the individual patient model coefficients described above. The model predicts that as the number of cases of thrombolysis increases in a hospital the chances that older patients and those arriving more than six hours after the onset of symptoms will receive t-PA decrease. For example, the odds ratios that older patients would receive t-PA in low-volume hospitals (15 cases/year) was OR 0.72 (95% CI 0.52–0.98) and decreased to OR 0.40 (95% CI 0.29–0.54) in a high-volume institution (90 cases/year). Patients presenting after six hours in low-volume hospitals had an OR of 0.78 (95% CI 0.53–1.16), compared with an OR of 0.44 (95% CI 0.34–0.57) in high-volume hospitals. Similarly, the importance of a cardiologist decision maker was attenuated in hospitals that had high (OR 1.37, 95% CI 0.86–2.20) vs low caseloads (OR 2.27, 95% CI 1.44–3.58). Patients who had low

blood pressure on admission had an increased probability of receiving t-PA independent of hospital-level variables.

The geographic location of a hospital had an important impact on two patient predictors. While both urban and rural hospitals gave t-PA more frequently to patients with prior myocardial infarction, this was more pronounced for urban centers (OR 2.86, 95% CI 2.00–4.08 vs OR 2.02, 95% CI 1.46–2.80). The biggest difference between urban and rural physicians was in the importance accorded to the electrocardiographic location of the infarction. An anterior myocardial infarction in a rural hospital increased the odds of receiving t-PA by 1.66, 95% CI 1.29–2.13, but this rose to 6.55, 95% CI 5.02–8.56 in urban hospitals.

If an odds ratio > 1.25 represents a meaningful difference in the selection criteria for a thrombolytic agent, this model predicts that physicians practicing in 80% of hospitals would favor giving t-PA to younger patients. Similarly, the percentages of hospital policies that would preferentially apply t-PA (odds ratio > 1.25) in cases of anterior infarctions, previous infarctions, patients with low blood pressures, and early presenters are 92%, 83%, 95%, and 78%, respectively.

Discussion

The hierarchical analysis presented here has provided insights into the patient, physician, and hospital characteristics determining the choices of thrombolytic agents for patients with acute myocardial infarction in Quebec hospitals. The independent patient characteristics that predicted an increased probability of receiving t-PA included younger age, an anterior myocardial infarction, low presenting blood pressure, a previous myocardial infarction, arrival within six hours of symptom onset, and a cardiologist decision maker. It is interesting to compare these decisions with ''evidence-based'' results from the medical literature.

A synthesis of the comparative trials of the two main thrombolytics, SK and t-PA, suggests no or little difference in mortality between the two agents.[9,33] However, one trial[4] did find a mortality difference in favor of t-PA, and the uniqueness of this trial's accelerated protocol and its non-comparability with previous studies has been emphasized. The variation in t-PA utilization may reflect a balance between this conflicting evidence of increased efficacy, societal opinions about escalating medical costs, and the importance of cost–effectiveness (t-PA is approximately eight times more expensive than SK).

The proportion of use of t-PA in this registry was 31.8%, which is intermediate between American and European rates. This result is not unexpected, since while the universal health care plan in Quebec is similar to those in most European countries, local practice patterns may be influenced by Canada's geographic proximity to the United States, and by the long-standing relationship of collaborative research and postgraduate training between these two countries.

The GUSTO trial[4] had a constant 14% relative reduction of adverse events across patient subgroups with t-PA, but the largest absolute gain was for patients with anterior myocardial infarction, due to their higher baseline mortality (1.9% absolute reduction in death rate compared with 0.9% for the whole trial). A prior MI is also a significant predictor for increased mortality, and the absolute advantage of t-PA is again maximized within this group.[34] Therefore, current evidence suggests that the most appropriate use of t-PA is for patients with anterior or previous MI, and Quebec physicians seem to concur, having adopted such a selective strategy. Finally, the GUSTO trial randomized patients only within six hours of symptom onset, and no trial-based evidence exists to suggest a difference in outcomes be-

Table 2 • Independent Predictors of t-PA Administration (Odds Ratios and 95% Credible Intervals) Based on Non-hierarchical and Simple Hierarchical Models (n = 1,165)*

	No Hierarchy (Fixed-effect Model)			Simple Hierarchy (Random-effects Model)		
	Posterior Mean of the β Coefficient	Odds Ratio (e^{β})	Odds Ratio 95% CI	Posterior Means of the β Coefficient	Odds Ratio (e^{β})	Odds Ratio 95% CI
Age > 65 years	−0.403	0.67	0.58–0.77	−0.614	0.54	0.44–0.67
Anterior myocardial infarction	0.802	2.23	1.95–2.56	1.100	3.00	2.42–3.73
Time from pain onset to thrombolysis > 6 hours	−0.563	0.57	0.47–0.69	−0.587	0.56	0.44–0.71
Previous myocardial infarction	0.814	2.26	1.92–2.65	0.826	2.28	1.82–2.86
Low BP (<120 mm Hg systolic)	0.629	1.88	1.62–2.17	0.741	2.10	1.75–2.51
Cardiologist decision maker	0.397	1.49	1.30–1.70	0.595	1.81	1.32–2.49
Sex	0.038	1.04	0.89–1.21	−0.019	0.98	0.80–1.20

*95% credible interval (CI) is the Bayesian analog to the confidence interval. Note that the two types of credible intervals above have different interpretations. In the fixed-effects model, the CI reflects uncertainty about each independent parameter value due to within-hospital variation. In the random-effects model, the 95% CI reflects uncertainty due to both within- and between-hospital variations.

tween thrombolytic agents when given later. The physicians in our data appreciated this lack of knowledge, as evidenced by the 42% reduction in the probability of receiving t-PA beyond six hours after onset.

Physicians clearly have a tendency to choose t-PA for hypotensive patients. SK may cause transitory hypotension, which usually responds to a slight reduction in the rate of administration and volume expansion and should not prevent its administration.[5] On the other hand, hypotension may also be a marker for cardiogenic shock, and physicians may have again interpreted this situation as potentially offering a high absolute benefit for t-PA. However, it must be noted that, although underpowered, the GUSTO data did not show any mortality advantage with t-PA for patients in Killip class IV.[35]

In GUSTO, the absolute reduction in mortality with t-PA was relatively constant across different age strata (1.1% vs 1.3% reduction in those younger and older than 75, respectively), but the confidence intervals surrounding the net clinical benefit were wide and all trials have demonstrated an increased rate of hemorrhagic stroke with t-PA, particularly in the elderly. An accompanying GUSTO economic analysis[36] suggested that treatment with t-PA was less cost-effective in younger patients. The cost–effectiveness ratios ($/year of life saved) for anterior MI were $125,000, $45,000, $20,000, and $13,000 for patients under 40, 41–60, 71–75 and over 75, respectively. Clearly, Quebec physicians were not influenced by this cost-effectiveness analysis, as elderly patients had a significant 33% reduction in the probability of receiving t-PA (OR 0.67, 95% CI 0.58–0.77). Since our data were collected only shortly after the GUSTO cost analysis was published, it is possible that the timing of our study limited the physicians' ability to absorb this information beforehand. Furthermore, this policy of selectively treating younger patients with t-PA has been recommended by leading authorities.[37]

There is no clear explanation for the independent role of a cardiologist decision maker with respect to the increased probability of receiving t-PA. It has been suggested that cardiologists are more aware of and make more frequent use of clinically proven, evidence-based medical therapies, including thrombolysis, compared with primary care physicians.[22,23] In this cohort, however, all patients received thrombolysis. The cardiologist involvement may be a marker for residual unmeasured high-risk patient characteristics. Alternatively, cardiologists may tend to less preferentially select patients for treatment with the more expensive agent. As medical specialists, cardiologists perhaps face diverse pressures to use the most reputed efficacious treatment available, regardless of cost.

There has been considerable debate in the medical literature as to the presence of a gender bias in the treatment of AMI.[38,39] Reassuringly, no evidence of gender bias was found in the selection of thrombolytic agent in our data.

This study also examined the roles of different hospital attributes on the choice of thrombolytic agent. In general, as the thrombolytic caseload increased, the physician practice was to be increasingly more selective in the administration of the more expensive agent to patients perceived as having the most to gain. In this regard, while overall physician practice for this cohort was to preferentially use t-PA for younger patients and those presenting within six hours, these tendencies were more pronounced at high-volume institutions. In high-volume hospitals, physicians also seemed to behave more homogeneously, and consequently the unexplained independent role of a cardiologist decision maker was muted.

Urban physicians behaved differently than their rural colleagues, independent of caseload. The reason for this difference is unknown, and it could represent different physician beliefs as to the probability of a true efficacy difference between agents, or as to the importance of the cost–effectiveness issues. Possibly rural doctors have listened most closely to regional guidelines, which have stressed the importance of rapid administration over the choice of thrombolytic agent.[11,40] One could also speculate that urban physicians have more contact with their U.S. colleagues and with drug company–sponsored events, which may influence their practice patterns, or it may be simply that budget constraints are more severe in rural hospitals.

Several limitations of this study should be mentioned. Unmeasured variables may have resulted in residual confounding of our model estimates. For example, among patient-level characteristics, previous SK exposure was not recorded, and among hospital characteristics we did not measure whether hospitals had specific limits on the funds available for thrombolytics, an unlikely possibility in our experience. Also, although there was no obvious systematic bias in the missing data, this may still be another source of bias. While the data for this registry were entered by trained research nurse coordinators and validated when entered into the database, logistic constraints prevented external validation of the source documents from being performed. Finally, these data do not permit any conclusions about the appropriateness of thrombolysis in this cohort, which would require blinded data extraction from the medical charts to be analyzed by an expert panel using accepted national treatment guidelines.[41]

In conclusion, Quebec physicians have adopted a

selective approach to the utilization of t-PA that appears more closely aligned to European practice than to U.S. practice. Physician decision making seemed predicated on the desire to maximize perceived absolute survival advantages. The medical literature generally, but not completely, confirmed the physicians' identification of high-risk patients with the most potential for gain. The physicians did not seem influenced by an economic analysis favoring t-PA administration for the elderly. Beyond patient characteristics, physician specialty and working environment impact clinical decision making significantly.

The executive branch of the Quebec Acute Coronary Care Working Group is comprised of Drs. Peter Bogaty (chairman), James Brophy, Franz Dauwe, Jean G. Diodati, Richard Gallo, Thao Huyhn Thanh, James Nasmith, Michel Nguyen, Normand Racine, and Pierre Théroux (past chairman). The organizational and administrative skills of Marie Andrée Seguin are gratefully acknowledged.

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APPENDIX

Hierarchical Model

Our full hierarchical model can be described by four stages: At the first stage, a separate logistic regression model is fit within patients at each hospital. The within-hospital model was

$$\begin{aligned}\text{logit}(p_{ij}) = {} & \beta_{0i} + \beta_{1i}\cdot \text{age}_{ij} + \beta_{2i}\cdot \text{old\_mi}_{ij} + \beta_{3i}\cdot \text{site}_{ij} \\ & + \beta_{4i}\cdot \text{time}_{ij} + \beta_{5i}\cdot \text{bp}_{ij} + \beta_{6i}\cdot \text{md}_{ij} + \beta_{7i}\cdot \text{gender}_{ij}\end{aligned}$$

where p_{ij} represents the probability that the jth subject at the ith hospital was administered t-PA, $\text{logit}(p_{ij}) = \log\left(\frac{p_{ij}}{1-p_{ij}}\right)$, $\beta_{0i}, \beta_{1i}, \ldots, \beta_{7i}$ represents the intercepts and the vectors of hospital-specific regression coefficients for hospital i, for the patient characteristics age (> or <65), old MI (yes/no), anterior ECG site (yes/no), presentation within six hours of symptom onset (yes/no), blood pressure (> or <120 systolic), cardiologist decision maker (yes/no) and gender, respectively.

At the second stage, the between-hospital variation about the intercept and each regression coefficient is modeled by a normal distribution so that

$$\beta_{ki} \sim \text{Normal}\,(\mu_{ki}, \sigma_k^2)$$

where β_{ki} represents the kth logistic regression parameter (k = 0,1,2. . .,7) in the ith hospital, which is assumed to follow a normal distribution with mean μ_{ki} and variance σ_k^2. Therefore, we recognize that the regression coefficients may vary from center to center according σ_k^2. If $\sigma_k^2 = 0$, then all β_{ki}s are the equal across hospitals and our model reduces to a standard (non-hierarchical) logistic regression. Conversely, larger values of σ_k^2 indicate larger between-hospital variations for the effects of parameter k. In our data there was evidence of variation between hospitals so $\sigma_k^2 > 0$ and this stage provided a more realistic model than simple logistic regression.

At the third stage, the between-hospital variation in each regression coefficient is explained by regressing the μ_{ki}s on hospital-specific characteristics, so that

$$\mu_{ki} = \alpha_k + \gamma_1\cdot \text{volume}_i + \gamma_2\cdot \text{location}_i + \gamma_3\cdot \text{status}_i$$

where μ_{ki} is the mean of the kth patient regression coefficient β_{ki} from the i different hospitals, γ_{1i}, γ_{2i}, γ_{3i} are the regression coefficients for the ith hospital characteristics, volume of activity, location (urban/rural), and status (tertiary vs non tertiary).

Finally, at the fourth stage, prior distributions are set for σ_k^2 and the above set of third-stage regression parameters. The prior distributions represent what was known a priori (before the data were analyzed) about the parameter values. We used non-informative prior distributions (all values have approximately equal probabilities), which contributed only negligible information, so that our final inferences are based almost exclusively on the information contained in the data.

An exact analytic solution for this complex model is impossible. Inferences were therefore carried out using the Gibbs sampler, a Markov-chain Monte Carlo approach to numerical integration,[42] wherein random samples from the marginal distribution of each parameter of interest are generated by intensive computer calculations. For each parameter, we used samples of size 10,000, which provided a high degree of accuracy in the final estimates. After ensuring convergence, empirical summary statistics can be formed and used to make inferences about the true values of the quantities of interest. This computational work was performed using BUGS software.[43]