Time to treatment with thrombolytic therapy: determinants and effect on short-term nonfatal outcomes of acute myocardial infarction

Evidence

Études

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Abstract

Objectives: To characterize the extent of delay in administration of thrombolytic therapy to patients with acute myocardial infarction (AMI) in Canada, to examine patient-specific predictors of such delay and to measure the effect of delay on short-term nonfatal cardiac outcomes.

Design: Secondary cohort analysis of data from the first international Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO-I) trial.

Setting: Sixty-three acute care hospitals across Canada.

Subjects: All 2898 Canadian patients with an AMI enrolled in GUSTO-I.

Main outcomes: Time before arrival at a hospital ("symptom-to-door" time) and time from arrival to administration of therapy ("door-to-needle" time) for patients who had an AMI outside of a hospital, in clinically relevant categories; proportions of patients with nonfatal, serious cardiac events, including shock, sustained ventricular tachycardia, ventricular fibrillation and asystole.

Results: Of the total number of patients enrolled, records were complete for 2708; 2542 of these patients (93.9%) had an AMI outside of a hospital. These 2542 patients presented a median 81 (interquartile range 50 to 130) minutes after the onset of symptoms, and the median time to treatment in hospital was 85 (interquartile range 61 to 115) minutes. Whereas a greater proportion of Canadian patients than of patients enrolled in GUSTO-I in other countries reached hospital within 2 hours of symptom onset (71.5% v. 61.2%, $p < 0.001$), a greater proportion of Canadian patients experienced in-hospital treatment delays of more than 1 hour (75.3% v. 57.1%, $p < 0.001$). In an analysis of all 2708 patients with complete records, both the unadjusted and adjusted odds of nonfatal cardiac events for those treated 4 to 6 hours after symptom onset were significantly higher than for those treated within 2 hours (odds ratio 1.60, 95% confidence interval 1.09 to 2.37).

Conclusion: After arrival at a hospital, Canadian patients enrolled in GUSTO-I received thrombolytic therapy more slowly than trial enrollees in other countries. Such delays are already known to decrease the rate of short-term survival after AMI. The findings further show that long time to treatment also increases the odds of nonfatal, serious cardiac events. Hospitals and physicians caring for patients with AMI should routinely assess whether and how they can improve door-to-needle times.

Résumé

Objectifs : Définir l'ampleur du retard dans l'administration d'une thérapie thrombolytique aux victimes d'un infarctus aigu du myocarde (IAM) au Canada, analyser des prédicteurs rattachés aux patients de ces retards et mesurer l'effet du retard sur les résultats cardiaques non mortels à court terme.

Conception : Analyse par cohortes secondaires de données tirées de la première étude internationale sur l'utilisation globale de la streptokinase et des tPA pour artères coronariennes bloquées (GUSTO-I).

Contexte : Soixante-trois hôpitaux de soins actifs au Canada.

Sujets : Les 2898 patients canadiens victimes d'un IAM qui ont participé à l'étude GUSTO-I.

Principales mesures des résultats : Temps écoulé avant l'arrivée à un hôpital (temps écoulé «entre les symptômes et l'arrivée à la porte») et temps écoulé entre l'arrivée et l'administration du traitement (temps écoulé «entre l'arrivée et la piqûre») dans le cas des patients qui ont été victimes d'un IAM en dehors d'un hôpital, dans les catégories pertinentes sur le plan clinique; proportion des patients victimes d'incidents cardiaques sérieux non mortels, y compris choc, tachycardie ventriculaire soutenue, fibrillation ventriculaire et asystole.

Résultats : Les dossiers de 2708 des patients inscrits à l'étude étaient complets. De ce nombre, 2542 (93,9 %) avaient été victimes d'un AIM en dehors d'un hôpital. Chez ces 2542 patients, la médiane du temps écoulé entre l'apparition des symptômes et l'arrivée à l'hôpital s'est établie à 81 (fourchette interquartiles de 50 à 130) minutes et celle du temps écoulé avant le traitement à l'hôpital s'est établie à 85 (fourchette interquartiles de 61 à 115) minutes. Si la proportion des patients canadiens qui sont arrivés à l'hôpital moins de 2 heures après l'apparition des symptômes est plus importante que celle des patients d'autres pays inscrits à l'étude GUSTO-I (71,5 % c. 61,2 %, $p < 0,001$), celle des patients canadiens qui n'ont été traités qu'après plus d'une heure à l'hôpital est plus élevée aussi (75,3 % c. 57,1 %, $p < 0,001$). Une analyse des 2708 dossiers complets a révélé que les risques non corrigés et les risques corrigés d'incidents cardiaques non mortels chez les sujets traités de 4 à 6 heures après l'apparition des symptômes étaient beaucoup plus élevés que chez les sujets traités dans les 2 heures (risque relatif de 1,60, intervalle de confiance à 95 % de 1,09 à 2,37).

Conclusion : Après leur arrivée à un hôpital, les patients canadiens inscrits à l'étude GUSTO-I ont reçu une thérapie thrombolytique plus tard que les patients d'autres pays inscrits à l'étude. On sait déjà que ces retards réduisent le taux de survie à court terme après un IAM. Les résultats indiquent en outre que la durée prolongée de l'attente d'un traitement augmente aussi les risques d'incidents cardiaques sérieux non mortels. Les hôpitaux et les médecins qui traitent des patients victimes d'un IAM devraient évaluer régulièrement s'ils peuvent réduire le temps écoulé entre l'arrivée du patient et l'administration du traitement et comment ils pourraient le faire.

The first international Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO-I) trial examined the benefits of thrombolytic therapy. It enrolled a total of 41 021 patients from 15 countries presenting with an acute myocardial infarction (AMI) within 6 hours of the onset of symptoms.[1] Almost 3000 patients treated at 63 hospitals across Canada were enrolled in the study. Apart from its conclusions about choice of thrombolytic agent, the study confirmed that greater survival benefit with thrombolysis occurs with attainment of vessel patency as soon as possible after symptom onset.

A survival benefit is observed when therapy is administered up to 12 hours after symptom onset.[2,3] However, the largest effect is obtained when treatment is administered early, and the benefit is attenuated with time.[4] Thus, it is now recommended that thrombolytic therapy be administered within 30 minutes of a patient's arrival at a hospital.[5]

Studies conducted in the United States,[6] Britain,[7] Italy[8] and New Zealand[9] have documented delays in treatment for patients presenting with an AMI. However, the extent of treatment delays in Canada is unknown.

This secondary analysis of Canadian data from GUSTO-I was undertaken primarily to characterize the extent of, and patient-specific factors associated with, delayed administration of thrombolytic therapy to patients with an AMI. We address separate components of delayed treatment: time from symptom onset to presentation at the hospital ("symptom-to-door" time) and time from registration in the emergency department to treatment ("door-to-needle" time). Symptom-to-door time may be related to various patient factors that were not studied in the GUSTO-I trial, such as knowledge, attitudes and beliefs of patients and their family members, or distance to the nearest hospital. Our analysis is therefore limited to how demographic, historical and clinical characteristics are related to symptom-to-door time. Door-to-needle time reflects the efficiency of the health care team and, if

unduly long, highlights a need for providers to determine whether and how they can improve their care. We first compared door-to-needle time in Canada with that in other nations and then delineated, through multivariate analysis, which patients are most at risk of delayed administration of thrombolytic therapy.

With respect to outcomes, Lee and associates,[10] drawing on the entire GUSTO-I data set, developed a multivariate model, which controls for confounding effects, to predict rates of death within 30 days after an AMI. Their analysis confirmed the independent effect of treatment delay on the odds of death within 30 days. Time to treatment has also been inversely correlated with preservation of left ventricular function,[11–14] but other nonfatal outcomes have received little attention in the research literature. Therefore, to delineate this type of harm attributable to delayed treatment, we also examined the independent effects of time to treatment on a set of specified nonfatal outcomes among the Canadian patients.

Methods

Subjects and setting

There were 2898 patients with an AMI, treated at 63 acute care hospitals across Canada, enrolled in GUSTO-I. Patients were enrolled up to 6 hours after symptom onset, and therapy was occasionally delayed more than 8 hours after symptom onset. However, since the stated intent of the trial was to examine outcomes among patients treated within 6 hours of symptom onset, in our initial analysis we examined only the patients treated within 6 hours of self-reported symptom onset. All patients treated after 6 hours or more were included in a subsequent sensitivity analysis.

Analysis

General issues

Baseline demographic and clinical data were tabulated for the entire sample, regardless of whether the patients were outside of a hospital or inpatients at the time of the AMI. All patients were included in the examination of the effect of overall time to treatment on outcomes. For specific consideration of symptom-to-door and door-to-needle times, we included only those who were not in a hospital when the AMI occurred. The unpaired Student's *t*-test or analysis of variance (ANOVA) was used to compare means. Categorical variables were analysed with the χ^2 test or, when cell counts were low, with Fisher's exact test. All analyses were conducted with SAS (SAS Institute, Carey, NC).

Delayed treatment

Because the clinical importance and measurement of a few minutes' difference in time to treatment are uncertain, we categorized time to treatment as within 2 hours, from more than 2 to 4 hours or from more than 4 to 6 hours after symptom onset. The same categories were used to examine symptom-to-door times among patients who had an AMI outside of a hospital. For comparative purposes, the GUSTO-I Steering Committee provided us with limited, unpublished data on these times for all study subjects excluding those in Canada; data on median delays were also provided for subjects in the United States specifically. We conducted a straightforward univariate analysis of patient factors and their relation to symptom-to-door time. We included only demographic, clinical and historical factors, and we did not report physician-defined factors such as Killip class, location of the infarct, systolic blood pressure and pulse rate upon admission or peak creatinine phosphokinase level.

To examine predictors of delayed in-hospital treatment (door-to-needle time), we excluded patients who were in hospital when the AMI occurred and categorized door-to-needle time as less than 30 minutes, 30 minutes to 1 hour, more than 1 hour to 2 hours and more than 2 hours. After a univariate analysis, all variables significantly associated with treatment delay ($p < 0.05$) were included in a multiple logistic regression analysis to determine which patient factors were independently associated with delay. For simplicity, the dependent variable in the regression analysis was whether patients were treated within 30 minutes (the recommended door-to-needle time in Canada[5]).

Effect of delay on outcomes

We examined nonfatal but life-threatening cardiac events, a composite end point consisting of shock, sustained ventricular tachycardia, ventricular fibrillation or asystole. Individually, these events are important but infrequent medical emergencies that are not traditionally reported as primary end points; however, they are of obvious interest to clinicians, and their relation to time to thrombolytic therapy has not previously been determined. We designed the composite end point to augment statistical power. We calculated unadjusted odds ratios (ORs) for this end point among patients with an overall time to treatment of more than 2 hours to 4 hours and of more than 4 hours to 6 hours versus 2 hours or less. Next, we developed a multiple logistic regression model that did not include time-to-treatment variables to determine patient factors that independently predicted statistically significant adverse outcomes. Time to treatment was then forced into the model, and adjusted ORs of nonfatal, seri-

ous cardiac events were computed for time effects and other significant patient variables.

Results

Study population

Of the 2898 Canadian patients enrolled in GUSTO-I, full information on time to treatment was available for 2839 (98.0%). Of these, 131 were excluded because of prolonged treatment delay (more than 6 hours after symptom onset) or missing data on the primary outcomes of interest. The remaining 2708 patients (93.4%) constituted the available sample for analysis. Of these, 2542 had an AMI outside of a hospital and were considered in the analyses of determinants of delay, 158 were inpatients when they had an AMI and 8 could not be characterized owing to missing or erroneous hospital admission information. However, there was sufficient information to include all 2708 in the analyses of overall time to treatment and outcomes.

Patient demographic and clinical features

Baseline demographic and clinical features of the overall sample are provided in Table 1. Details concerning the comparative profiles of patients who were inpatients versus those outside of a hospital when the AMI occurred are available upon request.

Components of delayed treatment and international comparisons

The median overall time to treatment for the 2708 Canadian patients enrolled in GUSTO-I and included in this study was 175 (interquartile range [IQR] 130 to 235) minutes. Patients whose symptoms began when they were outside of a hospital took a median 81 (IQR 50 to 130) minutes to arrive at the hospital (symptom-to-door time). There was a further median treatment delay of 85 (IQR 61 to 115) minutes after hospital admission (door-to-needle time). Long symptom-to-door and door-to-needle times often affected the same patients. As a result, the median total time from symptom onset to thrombolytic therapy was 180 (IQR 135 to 240) minutes for patients whose symptoms began while they were outside of a hospital.

Compared with GUSTO-I patients in other nations (Table 2), the proportion of Canadian patients who presented in the earlier time categories was significantly higher, but the converse was true with respect to the door-to-needle time. Compared specifically with US patients, the median symptom-to-door time was 81 minutes in Canada versus 85 minutes in the United States, but the door-to-needle times were 85 minutes and 66 minutes respectively (unpublished data: the GUSTO-I Steering Committee, 1994).

Table 1: Demographic and clinical characteristics of the 2708 patients enrolled in the GUSTO-I trial in Canada treated within 6 hours and for whom information was complete

Characteristic	Mean (and standard deviation) or % of patients affected*
Age, yr	60.7 (12.1)
Systolic blood pressure on admission, mm Hg	130.0 (22.9)
Pulse on admission, beats per minute	74.1 (16.9)
Peak creatinine phosphokinase level, IU	2183.5 (1896.8)
Sex	
Male	76.2
Female	23.8
Diabetes mellitus	14.1
Hyperlipidemia	29.3
Smoking	73.4
Hypertension	32.8
Family history of coronary artery disease	46.4
History of cardiac disease or procedure	
Acute myocardial infarction (AMI)	16.7
Angina	38.3
Percutaneous transluminal coronary angioplasty	2.5
Coronary artery bypass grafting	3.7
Killip class	
I	86.7
II	11.6
III	1.4
IV	0.03
Location of AMI	
Anterior	39.7
Inferior	57.3
Other	2.9
In-hospital death	6.4
Death within 30 days of AMI	7.0
Nonfatal, serious cardiac event†	15.5
Shock	5.0
Sustained ventricular tachycardia or ventricular fibrillation	13.2
Second AMI	4.5
Recurrent ischemia	28.3
Congestive heart failure or pulmonary edema	19.1
Bradycardia	13.5
Stroke	1.4

*Percentages may not sum to 100 because of rounding.
†Includes shock, sustained ventricular tachycardia, ventricular fibrillation and asystole.

Factors related to delayed treatment

Patient characteristics examined for their effect on symptom-to-door time are shown in Table 3. Women tended to present later than men, and a slightly higher proportion of people 60 years of age and older presented 2 to 4 hours and more than 4 to 6 hours after symptom onset than less than 2 hours after symptom onset. Patients with diabetes mellitus or a previous coronary artery bypass graft also tended to present later. As noted earlier, we did not conduct a multiple regression analysis because of the lack of data about patients' travel time to the nearest hospital, family circumstances and access to transportation.

However, we developed a multivariate model for door-to-needle time. As shown in Table 4, the model showed that age, a history of hypertension and a higher pulse rate on admission were independent predictors of delay in administering thrombolytic therapy. By contrast, a history of angioplasty and inferior (versus anterior) AMI on presentation were both associated with substantially decreased odds of delayed thrombolytic therapy. Patient sex was not independently associated with treatment delay.

Nonfatal outcomes

Table 5 shows the specified fatal and nonfatal outcomes for the sample, stratified by overall time to treatment. There are clear time-related gradients for all of these outcomes. The difference in the risk of nonfatal but life-threatening outcomes was statistically significant only when these outcomes were treated as a single, composite variable. Table 6 shows the results of a multivariate analysis of this composite variable. This analysis confirmed an independent relation between delay in treatment and the odds of nonfatal serious outcomes, with a significant increase in the OR (1.60, 95% CI 1.09 to 2.37) for patients treated more than 4 hours after symptom onset.

Sensitivity analyses

In the sensitivity analyses we included all patients treated more than 6 hours after symptom onset, and in the multivariate analysis we included variables for which the significance level was 0.20 in the univariate analysis. These analyses yielded results similar to those of our main models (results available upon request).

Discussion

Treatment delays in Canada

These findings suggest that Canadian patients with an AMI arrived at a hospital relatively rapidly, compared with patients in other nations. However, treatment after arrival was slower in Canada than elsewhere. Only 3% of patients managed at GUSTO-I centres in Canada received a thrombolytic agent within 30 minutes, and more than 20% waited more than 2 hours. Long consent forms and additional research requirements for concurrent substudies may have delayed treatment; however, these exigencies were not unique to the Canadian setting.

This study did not compare the characteristics of enrollees in Canada to ascertain whether these characteristics account for the observed differences in time to treatment. However, a comparison of randomly selected Canadian and US GUSTO-I participants showed that the the cohorts were generally similar at entry.[15] A more recent article compared patients in GUSTO-I enrolled in the United States with those from other countries.[16] Sta-

Table 2: Delays in receiving thrombolytic therapy for patients participating in the GUSTO-I trial in Canada versus those in all other participating countries*

Time-to-treatment categories	No. (and %) of patients		
	Canada	Other participating countries	*p* value
Symptom-to-door time, hours	*n = 2 542*	*n = 35 844*	< 0.001
0 to 2	1 818 (71.5)	21 665 (60.4)	
> 2 to ≤ 4	646 (25.4)	11 795 (32.9)	
> 4	78 (3.1)	2384 (6.7)	
Door-to-needle time, minutes	*n = 2 542*	*n = 35 062*	< 0.001
< 30	72 (2.8)	656 (7.8)	
30 to 60	556 (21.9)	12 847 (36.6)	
> 60	1 914 (75.3)	19 559 (55.8)	

*Totals may not sum to overall GUSTO enrolment of 41 021 owing to incomplete data. Symptom-to-door time and door-to-needle time are defined in the text.

tistically significant differences in most baseline characteristics between the 2 groups were noted, but their clinical importance appeared highly questionable, and treatment times were not specifically considered.

One key caveat is that patients in the GUSTO-I study are not fully representative of the general population of Canadian patients presenting with an AMI. We have documented elsewhere that the GUSTO-I participants tended to be younger, were more often male and had fewer comorbid conditions than other patients with an AMI admitted to the same hospitals during the study period.[17] Furthermore, the GUSTO-I participants had to meet specific symptom and electrocardiographic criteria. However, the patient profile of GUSTO-I participants should have led to fewer, if any, delays in treatment than those experienced by all patients with an AMI.

Various sources of treatment delay in hospital have been identified.[5,7–9,18–20] They include waits for electrocardiographic services in the emergency department, preliminary bedside specialist consultation, unnecessary testing such as chest radiographs, long delays in obtaining the results of cardiac enzyme tests, transfers out of the emergency department to acute care units before thrombolytic therapy, and preparation of the infusion in an off-site pharmacy. Our study cannot identify which, if any, of these factors contributed to the surprisingly long door-to-

Table 3: Demographic and clinical characteristics of all 2542 patients who had an AMI outside of a hospital, stratified according to symptom-to-door time

	Symptom-to-door time, hours; no. (and %) of patients* unless otherwise specified			
Characteristic†	< 2 *n = 1818*	2–4 *n = 646*	> 4–6 *n = 78*	*p* value
Mean age (and standard deviation)	60.0 (11.9)	61.7 (12.7)	60.4 (12.3)	0.029
Age, yr				0.040
< 40	75 (4.1)	33 (5.1)	4 (5.1)	
≥ 40 to < 50	321 (17.7)	92 (14.2)	13 (16.7)	
≥ 50 to < 60	487 (26.8)	142 (22.0)	17 (21.8)	
≥ 60 to < 70	526 (28.9)	200 (31.0)	24 (30.8)	
≥ 70 to < 80	334 (18.4)	137 (21.2)	18 (23.1)	
≥ 80	75 (4.1)	42 (6.5)	2 (2.6)	
Sex				0.020
Male	1412 (77.7)	478 (74.0)	52 (66.7)	
Female	406 (22.3)	168 (26.0)	26 (33.3)	
Diabetes mellitus *n = 2537*	232 (12.8)	103 (16.0)	15 (19.2)	0.047
Hyperlipidemia *n = 2409*	527 (30.4)	159 (26.5)	23 (30.7)	0.191
Smoking *n = 2525*	1338 (74.1)	467 (72.9)	59 (76.6)	0.715
Hypertension *n = 2536*	563 (31.0)	219 (34.0)	26 (33.3)	0.366
History of AMI *n = 2542*	297 (16.3)	89 (13.8)	9 (11.5)	0.186
History of angina *n = 2529*	639 (35.3)	241 (37.6)	28 (35.9)	0.582
Previous percutaneous transluminal coronary angioplasty *n = 2539*	49 (2.7)	12 (1.9)	0	0.181
Previous coronary artery bypass grafting *n = 2539*	67 (3.7)	17 (2.6)	7 (9.0)	0.016

*Percentages may not sum to 100 because of rounding.
†For some characteristics, data on some patients were missing; in these cases, the number of patients for whom data were available is given.

needle times in Canadian centres participating in the GUSTO-I trial. Since GUSTO-I was completed, many hospitals in Canada have embarked on quality improvement programs that include attention to prompt use of thrombolytic therapy. The overall effect of these programs on mean door-to-needle time remains uncertain.

Subgroups most affected by treatment delays

The GUSTO-I results confirm that elderly people tend to arrive at a hospital later after symptom onset than younger people. The difference between women and men was larger and more significant than that between older and younger people. This suggests a need to educate elderly people and women, in particular, about the need for prompt presentation to hospital when they experience persistent chest pain.

Once patients reached hospital, age was an independent factor contributing to further delays. An odds ratio of 1.05 for each 5 years, for example, implies that the odds of delayed treatment are about 1.22 for a patient 60 years of age compared with a patient 40 years of age. Although sex was not an independent predictor of delay in treatment, age-related effects apply more to women than to men, since women with an AMI are older, on average, than men with this condition. We surmise that the delays in hospital resulted from the greater uncertainty about the diagnosis in elderly patients and from concerns about the risk of hemorrhagic stroke induced by thrombolytic therapy, which rises with age.[3]

Indeed, late presentation to hospital may contribute to further delays after admission; it may lead to uncertainty about treatment because later treatment reduces the benefit–risk ratio associated with thrombolytic therapy.[3] However, the mortality rate after an AMI is much higher among elderly people than among younger patients;[21–23] therefore, elderly people would be expected to experience the largest net gains from thrombolytic therapy.[3]

The reasons for faster treatment of patients with a previous angioplasty and slower treatment of those with previous hypertension are unclear. The delays related to anterior infarction and higher pulse rate on admission are of particular concern, since these risk factors are independently associated with poorer outcomes.[10]

In Canada, the Clinical Quality Improvement Network Investigators have sequentially tracked underuse of thrombolytic therapy and other effective drugs for AMI among elderly patients.[24–28] Their work has illustrated that management of elderly patients with an AMI can be improved by systematic quality-improvement processes.[28] In our view, such quality improvement is worthy of emulation; it could be extended specifically to the issue of time to treatment of AMI.

Table 4: Independent predictors* of delayed in-hospital treatment for the 2542 patients who had an AMI outside of a hospital

Predictor	Odds ratio (OR) (and 95% confidence interval [CI])	*p* value
Hypertension	1.29 (1.10–1.52)	0.002
Previous percutaneous transluminal coronary angioplasty	0.51 (0.31–0.82)	0.006
Pulse on admission (every increase of 10 beats per minute)	1.05 (1.00–1.10)	0.031
Age (every 5-year increase)	1.06 (1.03–1.09)	0.0003
Inferior (v. anterior) AMI	0.82 (0.70–0.96)	0.006

*Includes only variables significant at $p < 0.05$.

Table 5: Fatal and nonfatal cardiac outcomes for all 2708 patients with an AMI, stratified by overall time to treatment

Outcome	Time to treatment, hours; no. (and %) of patients: < 2 *n = 572*	2–4 *n = 1515*	> 4–6 *n = 621*	*p* value
In-hospital death	24 (4.2)	95 (6.3)	54 (8.7)	0.006
Death within 30 days of an AMI	24 (4.2)	106 (7.0)	59 (9.5)	0.002
Nonfatal, serious cardiac event*	70 (12.2)	241 (15.9)	109 (17.6)	0.033
Shock	22 (3.9)	77 (5.1)	36 (5.8)	0.302
Sustained ventricular tachycardia or ventricular fibrillation	59 (10.3)	207 (13.7)	91 (14.7)	0.061

*Includes shock, sustained ventricular tachycardia, ventricular fibrillation and asystole. Each patient with 1 or more of these outcomes was counted only once.

Relation between treatment delay and fatal and nonfatal outcomes

Our results confirm that longer times to treatment with a thrombolytic agent lead to higher risk of a nonfatal adverse event. This time effect was fairly stable, regardless of whether the model was controlled for patient variables. Lee and associates,[10] in a study of the GUSTO-I database, showed that age had a graded and marked effect on death within 30 days after an AMI. For comparative purposes only, we developed a similar multivariate model for Canadian patients (Table 7). Our findings were consistent with those of Lee and associates in direction and magnitude but did not reach statistical significance. The consistency of the findings gives us greater confidence in our country-specific analysis. Furthermore, in Canada, age effects on nonfatal but life-threatening outcomes were significant but only in a comparison of patients 80 years of age and older with those younger than 40. Thus, there were somewhat different predictors associated with mortality and with nonfatal outcomes. These findings illustrate the usefulness of examining such a composite

Table 6: Unadjusted and adjusted odds of nonfatal, serious events (shock, sustained ventricular tachycardia, ventricular fibrillation or asystole)

Predictor	Unadjusted OR (and 95% CI)	*p* value	Adjusted OR (and 95% CI)*	*p* value
Time to treatment, hours (v. ≤ 2)				
> 2 to ≤ 4	1.36(1.02–1.81)	0.036	1.29 (0.92–1.81)	0.142
> 4 to ≤ 6	1.53(1.10–2.11)	0.011	1.60 (1.09–2.37)	0.017
Systolic blood pressure on admission (every increase of 10 mm Hg)	NA†		0.90 (0.85–0.95)	0.0002
Pulse on admission (every increase of 10 beats per minute)	NA		1.15 (1.08–1.23)	0.0001
Bradycardia	NA		13.60(10.38–17.92)	0.0001
Age ≥ 80 yr (v. age < 40 yr)	NA		1.90 (1.14–3.17)	0.014
Peak creatinine phosphokinase level (every increase of 100 IU)	NA		1.01 (1.00–1.02)	0.001
Congestive heart failure or pulmonary edema	NA		1.91 (1.44–2.54)	0.0001

*Adjusted ORs are based on a logistic regression model that assessed the ability of time to treatment (forced into the model) to predict life-threatening cardiac events, with adjustment for all variables significant at $p < 0.05$.
†NA = not applicable.

Table 7: Unadjusted and adjusted odds of death within 30 days of AMI

Predictor	Unadjusted OR (and 95% CI)	*p* value	Adjusted OR (and 95% CI)	*p* value
Time to treatment, hours (v. ≤ 2)				
< 2 to ≤ 4	1.72 (1.09–2.71)	0.020	1.14(0.61–2.12)	0.68
< 4 to ≤ 6	2.40 (1.47–3.91)	0.0005	1.55(0.79–3.05)	0.201
Hypertension	NA		1.70 (1.11–2.58)	0.014
Killip class II (v. class I)	NA		2.48 (1.51–4.07)	0.0003
Killip class III or IV (v. class I)	NA		3.72 (1.38–10.02)	0.010
Shock	NA		13.09 (7.68–22.32)	0.0001
Sustained ventricular tachycardia or ventricular fibrillation	NA		5.30 (3.24–8.65)	0.0001
Bradycardia	NA		5.92 (3.57–9.80)	0.0001
Age, yr (v. < 40)				
≥ 60 to < 70	NA		2.34 (1.25–4.39)	0.008
≥ 70 to < 80	NA		6.89 (3.80–12.48)	0.0001
≥ 80	NA		15.25 (7.29–31.89)	0.0001
Inferior AMI (v. anterior AMI)	NA		0.36 (0.23–0.56)	0.0001

measure, which provides enhanced statistical power.

To prove that a relation exists between time to treatment and adverse outcomes, a study with a randomized design would be ideal. However, it would be unethical to delay thrombolytic therapy deliberately. In one trial, the investigators were able to compare prehospital and hospital-initiated thrombolytic therapy, but they found small time differences.[14] Hence, observational analyses with large samples remain the most powerful way to elucidate the effects of delayed treatment on the outcomes of AMI.

Conclusion

The 1994 update of the Canadian Consensus Conference on Coronary Thombolysis[29] recommended that thrombolytic therapy be initiated within 1 hour of a patient presenting to a hospital with AMI. Yet, in the Canadian arm of the GUSTO-I trial, 75% of patients received therapy more than 1 hour after arrival at a hospital. This rate was significantly higher than that in other countries. More recent recommendations suggest a treatment delay of no more than 30 minutes.[4] Earlier analyses have shown that shorter time to treatment reduces mortality rates, and our study confirms that this benefit extends to major nonfatal cardiac outcomes. Thus, there is an overwhelming case for reducing door-to-needle times in Canada. We urge clinicians and administrators to examine the management of AMI in their centres to ensure not only the maximal appropriate use of thrombolytic therapy but also its prompt use.

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