Effectiveness of a change in reperfusion strategy to primary percutaneous coronary intervention in a nonselected population

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BACKGROUND: Randomized controlled trials have established the clinical superiority of primary percutaneous coronary intervention (PCI) over fibrinolysis for ST segment elevation myocardial infarction (STEMI) in selected populations. However, the clinical effectiveness of the primary PCI strategy with modern adjunctive antiplatelet therapy deserves further evaluation.

OBJECTIVE: To validate results from randomized controlled trials in a nonselected Canadian population.

METHODS: A retrospective study of 243 consecutive patients who presented with a STEMI at a single academic centre was performed. Baseline characteristics, treatment strategies and in-hospital outcomes of patients treated in 2004 to 2005 (n=129) were compared with those of patients treated in 1999 to 2000 (n=114). Logistic regression was used to adjust for imbalanced baseline characteristics.

RESULTS: Patients in the 2004 to 2005 cohort versus those in the 1999 to 2000 cohort were older and more likely to be hypertensive and to present in Killip class 2 to 4. All of the patients treated in 2004 to 2005 underwent a primary PCI strategy compared with 32.5% in the 1999 to 2000 cohort. The in-hospital incidence of death, reinfarction or stroke was reduced from 21.9% in 1999 to 2000, to 15.5% in 2004 to 2005 (adjusted OR 0.462; P=0.055), largely due to a reduction in reinfarction (10.5% to 3.1%, adjusted OR 0.275; P=0.041). In-hospital mortality and stroke rates did not change significantly. The median length of stay was reduced from eight to six days in the recent cohort (P=0.002).

CONCLUSIONS: In the present nonselected population, the change in reperfusion strategy from fibrinolysis to primary PCI in the treatment of STEMI reduced the length of hospitalization by two days and was associated with an adjusted 54% relative reduction in adverse in-hospital events, which was largely due to a significant reduction in reinfarction.

Key Words: Angioplasty; Health outcomes; Myocardial infarction; Reperfusion

L'efficacité d'une modification de la stratégie de reperfusion de l'intervention coronaire percutanée primaire au sein d'une population non sélectionnée

HISTORIQUE : Des essais aléatoires et contrôlés ont établi la supériorité clinique de l'intervention coronaire percutanée (ICP) primaire par rapport à la fibrinolyse en cas d'infarctus du myocarde avec élévation du segment ST (IMÉS) dans des populations sélectionnées. Cependant, l'efficacité clinique de la stratégie primaire d'ICP associée à un traitement antiplaquettaire auxiliaire moderne mérite d'être évaluée plus en profondeur.

OBJECTIF : Valider les résultats d'essais aléatoires et contrôlés au sein d'une population canadienne non sélectionnée.

MÉTHODOLOGIE : Les auteurs ont procédé à une étude rétrospective menée auprès de 243 patients consécutifs qui avaient consulté à un seul centre universitaire en raison d'un IMÉS. Ils ont comparé les caractéristiques de départ, les stratégies de traitement et les issues en milieu hospitalier des patients traités entre 2004 et 2005 (n=129) à celles des patients traités entre 1999 et 2000 (n=114). Ils ont utilisé la régression logistique pour rajuster les caractéristiques de départ non équilibrées.

RÉSULTATS : Les patients de la cohorte de 2004 à 2005 par rapport à celle de 1999 à 2000 étaient plus âgés et plus susceptibles d'être hypertendus et de faire partie du stade 2 à 4 de Killip. Tous les patients traités en 2004 et 2005 ont subi une stratégie primaire d'ICP par rapport à 32,5 % des patients de 1999 et 2000. L'incidence de décès, de nouvel infarctus ou d'accident vasculaire cérébral (AVC) en milieu hospitalier a chuté de 21,9 % en 1999 et 2000 à 15,5 % en 2004 et 2005 (RRR 0,462; P=0,055), en grande partie à cause d'une réduction des nouveaux infarctus (de 10,5 % à 3,1 %, RRR 0,275; P=0,041). Les taux de décès et d'AVC en milieu hospitalier n'ont pas changé de manière significative. La durée médiane d'hospitalisation est passée de huit à six jours dans la récente cohorte (P=0,002).

CONCLUSIONS : Dans la présente population non sélectionnée, le passage de la stratégie de reperfusion par fibrinolyse à une ICP primaire pour traiter l'IMÉS a réduit la durée d'hospitalisation de deux jours et s'associait à une réduction rajustée relative de 54 % des événements néfastes en milieu hospitalier, imputable en grande partie à une diminution considérable des nouveaux infarctus.

The treatment of myocardial infarction has tremendously evolved in recent years. Primary percutaneous coronary intervention (PCI) has been shown to be superior to thrombolytic therapy in the prevention of recurrent ischemic events or death in several randomized controlled trials (RCTs) (1-8) in selected populations, and is currently the preferred reperfusion strategy for the management of ST segment elevation myocardial infarction (STEMI). However, the generalizability of those RCT findings to actual clinical practice is often limited. Applying a primary PCI

strategy according to current guidelines (9) in the real-life environment remains difficult to achieve. In the United States, only 29.4% of patients received primary PCI within a door-to-balloon time of less than 90 min (10), which is the current recommended time. Another recent study performed in Quebec hospitals (11) showed a median door-to-balloon time of 109 min in PCI hospitals, with 35.5% of patients achieving recommended delays.

In May 2002, following presentation of the results from the DANish trial in Acute Myocardial Infarction-2 (DANAMI-2) (7), a decision

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TABLE 1
Baseline characteristics of patients

Characteristics	1999 to 2000 cohort* (n=114)	2004 to 2005 cohort† (n=129)	P
Age, mean $\pm$ SD, years	59.1 $\pm$ 12.9	64.8 $\pm$ 13.0	<0.001
Male sex, %	64.9	57.4	0.230
Hypertension, %	39.5	58.1	0.004
Dyslipidemia, %	28.9	50.4	<0.001
Diabetes, %	20.2	22.5	0.660
Current or past smoker, %	81.6	70.5	0.045
Anterior wall infarct, %	42.1	45.7	0.480
Killip class, %			
1	77.2	66.7	0.069
2	7.9	16.3	0.047
3	6.1	8.5	0.480
4	8.8	8.5	0.950

*Period from July 1999 to June 2000; †Period from April 2004 to March 2005

was made at the Centre hospitalier de l'Université de Montréal (Montréal, Québec) to use primary PCI as the sole reperfusion strategy for acute STEMI management. Whether this change in our reperfusion strategy led to similar benefits as those observed in RCTs remains uncertain. Because the vast majority of randomized data were obtained in European countries or in the United States, no retrospective data on the impact of primary angioplasty in Canada were available and, given recent concerns about nonoptimal door-to-balloon delays, we decided to undertake the present health services study to evaluate the short-term clinical effectiveness of a change in reperfusion strategy in the treatment of STEMI in a nonselected population in the context of real-life Canadian medical care.

METHODS

Patient population

The present study was conducted in a large tertiary Canadian academic centre that performs more than 3000 angioplasties per year, of which 18% are performed after regular working hours. Only patients who presented with a STEMI and who also received reperfusion therapy were considered. From April 2004 to March 2005, a total of 129 consecutive patients presented directly to the emergency room with STEMI and received reperfusion therapy. They were compared with 114 consecutive patients who presented with STEMI to the emergency room from July 1999 to June 2000. Patients were identified through the catheterization laboratory database and the central hospital archiving system after detailed review of their hospital charts. Patients were considered to have a STEMI if their initial electrocardiogram exhibited ST elevation in a plausible clinical context, according to currently available definitions (12).

Data collection

Baseline clinical characteristics, treatment strategies and in-hospital clinical outcomes were collected through detailed chart abstraction. Data from the 1999 to 2000 cohort were abstracted by cardiologists of the service, as part of a detailed quality of care analysis performed in 2003, under the supervision of one of the coauthors (SR). The latest cohort data were abstracted by a single physician (AM), using similar data abstraction forms. All data were subsequently entered into a database and denormalized to protect patient confidentiality. Because patients were first identified from the catheterization laboratory database, data from STEMI patients who did not undergo any reperfusion strategy were not available. The retrospective data abstraction was approved by the institution's Director of the Professional Services.

Reperfusion strategies

During the 1999 to 2000 time period, the reperfusion strategy consisted of fibrinolysis (either streptokinase or alteplase) or primary

angioplasty. The decision was left to the attending emergency physician or cardiologist. Thienopyridine agents were not systematically used and the decision to prescribe a glycoprotein IIb/IIIa inhibitor was left to the attending physician. In the 2004 to 2005 cohort, the reperfusion strategy consisted exclusively of primary PCI delivered 24 h per day, seven days per week. A stent was implanted when possible and clopidogrel was systematically used before or after stent implantation. Use of glycoprotein IIb/IIIa inhibitors was strongly encouraged, although the final decision was left to the attending interventional cardiologist.

Primary and secondary outcomes

The primary outcome was a composite of in-hospital death, reinfarction or stroke. Reinfarction was defined as an increase of cardiac biomarkers by at least 50%, associated with chest discomfort or ischemic electrocardiogram changes. Stroke was defined as any focal or global neurological deficit lasting more than 24 h. Secondary outcomes included the components of the primary outcome measure, fibrinolysis failure (which was considered if a less than 50% decrease in ST segment elevation was documented at 90 min), Thrombolysis in Myocardial Infarction (TIMI) major bleeding events, left ventricular ejection fraction at discharge and hospital length of stay.

Statistical analyses

All analyses were performed according to the intention-to-treat principle. Datasets of the two cohorts were merged and internal verifications were performed for data consistency and adequacy. Baseline characteristics of the two cohorts were compared using the *t* test for continuous variables and the χ^2 test for categorical variables. Data on in-hospital outcomes were analyzed using a logistic regression model, adjusting for the following a priori identified baseline characteristics: age, sex, hypertension, dyslipidemia, diabetes, current smoking or a history of smoking, myocardial infarction territory, Killip class and period of treatment (1999 to 2000 versus 2004 to 2005). Lengths of stay were compared using the nonparametric median two-sample test. Assuming an expected 45% RR reduction in the primary outcome of in-hospital death, reinfarction or stroke as seen in the DANAMI-2 trial (7), the power of the present study to detect such a difference in the 2004 to 2005 cohort was approximately 60%. A two-sided probability value of less than 0.05 was considered to be statistically significant. Analyses were performed using SAS version 9.1 (SAS Institute Inc, USA).

RESULTS

Patient characteristics

Significant differences were noted between the baseline characteristics of the two cohorts of patients (Table 1). Patients treated in 2004 to 2005 were older than those treated in 1999 to 2000 (64.8 $\pm$ 13.0 years of age versus 59.1 $\pm$ 12.9 years of age; *P*<0.001). Diagnoses of hypertension (58.1% versus 39.5%; *P*=0.004) and dyslipidemia (50.4% versus 28.9%; *P*<0.001) were documented more frequently in the 2004 to 2005 cohort. Current or past tobacco use was less frequently reported in the 2004 to 2005 cohort (70.5% versus 81.6%; *P*=0.045) and the proportion of patients with diabetes was similar in both groups (22.5% versus 20.2%; *P*=0.660). Anterior wall infarct was present in slightly less than 50% of patients (45.7% versus 42.1%; *P*=0.480) and there was a trend toward fewer Killip class 1 infarcts in the 2004 to 2005 cohort (66.7% versus 77.2%; *P*=0.069), although the occurrence of cardiogenic shock was similar in both groups (8.5% versus 8.8%; *P*=0.950).

Reperfusion strategies and time intervals

All patients in the 2004 to 2005 cohort were treated in the context of an emergent primary PCI strategy (Table 2). In the 1999 to 2000 cohort, approximately one-third of the patients were treated with a primary PCI strategy and the rest with fibrinolysis, mostly with streptokinase or alteplase. Failure to achieve reperfusion occurred in 18.2%

TABLE 2
Reperfusion strategies

Strategy	1999 to 2000 cohort* (n=114), %	2004 to 2005 cohort† (n=129), %	P
Primary PCI	32.5	100.0	<0.0001
Fibrinolysis	67.5	0	
Streptokinase	33.3	0	
Alteplase	33.3	0	
Retepase	0.9	0	
Failed fibrinolysis	18.2	0	
Glycoprotein IIb/IIIa inhibitors	25.4	65.1	<0.0001
Abciximab	14.9	6.2	
Eptifibatide	3.5	41.1	
Tirofiban	7.0	17.8	
Thienopyridines	49.1	91.5	<0.0001
Cardiac catheterization during hospitalization, %	78.1	100.0	<0.0001

*Period from July 1999 to June 2000; †Period from April 2004 to March 2005.
PCI Percutaneous coronary intervention

of fibrinolysis attempts. All patients with fibrinolysis reperfusion failure underwent cardiac catheterization for rescue angioplasty. Overall, almost 80% of patients in the 1999 to 2000 cohort underwent cardiac catheterization during the index hospitalization. Antiplatelet therapies significantly changed over time. Thienopyridine agents were used in a majority of patients in the 2004 to 2005 cohort and in only one-half of those from the 1999 to 2000 cohort (91.5% versus 49.1%; $P<0.0001$). Glycoprotein IIb/IIIa inhibitors were also used much more frequently in the 2004 to 2005 cohort (65.1% versus 25.4%; $P<0.0001$). Symptoms-to-door delays were similar in both groups; approximately one-half of patients presented within the first 2 h of symptom onset (Table 3). In the 2004 to 2005 cohort, median door-to-balloon time was 116.5 min for the primary PCI procedure and only 23.4% of the patients were treated within 90 min. Unfortunately, door-to-reperfusion times for both fibrinolysis and primary angioplasty in the 1999 to 2000 cohort were not available.

In-hospital outcomes

Primary and secondary end points are shown in Table 4. The crude primary end point was reduced from 21.9% in the 1999 to 2000 cohort to 15.5% in the 2004 to 2005 cohort (unadjusted OR 0.653; $P=0.200$). However, after adjustment for the various imbalanced risk factors, a favourable trend was observed, with a 54% reduction in the primary end point in the 2004 to 2005 cohort compared with the 1999 to 2000 cohort (adjusted OR 0.46; 95% CI 0.21 to 1.02; $P=0.055$). This effect was largely attributed to a significant reduction in the rates of reinfarction (adjusted OR 0.28; 95% CI 0.08 to 0.95; $P=0.041$). With the available sample size, no significant reduction of in-hospital mortality (adjusted OR 0.67; 95% CI 0.25 to 1.79; $P=0.422$) or stroke rate was observed. TIMI major bleeding was also reduced by 33% (adjusted OR 0.67; 95% CI 0.21 to 2.10; $P=0.488$). In the 2004 to 2005 cohort, two-thirds of bleeding cases were associated with the catheterization procedure, whereas the other one-third consisted of gastrointestinal tract bleeding. The median length of stay was reduced from eight days to six days ($P=0.002$). The left ventricular ejection fraction at discharge was similar between the two cohorts (46.4% versus 46.7%; $P=0.472$).

DISCUSSION

A change in the preferred reperfusion strategy for the management of STEMI in a nonselected population in favour of exclusive primary PCI, combined with an aggressive use of antiplatelet agents and routine stenting, was associated with a reduction in the primary end point of in-hospital death, reinfarction or stroke. This positive effect was observed despite relatively long door-to-balloon time delays. Only 23.4% of patients in the 2004 to 2005 cohort were treated within

TABLE 3
Time delays

Time delay	1999 to 2000 cohort* (n=114)	2004 to 2005 cohort† (n=129)
Symptom onset to presentation time, %		
0 h to 2 h	43.0	53.4
>2 h to 4 h	22.8	20.2
>4 h to 6 h	13.1	8.5
>6 h	18.4	17.8
Not available	2.6	0
Door-to-balloon time, min‡	N/A	116.5 (91 to 160.5)

*Period from July 1999 to June 2000; †Period from April 2004 to March 2005;

‡Data presented as median (interquartile range). N/A Not available

90 min of presentation, which is the current standard. Nevertheless, after adjustment for the many cofactors that disadvantaged the more recent cohort, such as a higher age, a slightly lower proportion of Killip 1 infarct and more frequent risk factors, the 54% RR reduction almost reached the conventional level of statistical significance. This effect was largely driven by a major adjusted RR reduction (72%) in reinfarction rate.

The magnitude of the benefit observed was similar to previously published RCTs. In the DANAMI-2 trial (7), of the 443 patients who presented in invasive treatment centres, primary PCI was associated with a 45% RR reduction in the composite end point of death, reinfarction and disabling stroke at 30 days. This large effect was also mostly driven by an 85% reduction in reinfarction rate. In the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) trial (6), a 42% RR reduction in the similar composite end point at discharge was achieved with primary PCI, which was again largely driven by a significant reduction in the reinfarction rate. Thus, the results of our study are reassuring in demonstrating that the clinical benefits of primary PCI in the management of STEMI achieved in RCTs are reproducible to a similar extent when applied to a real-life clinical setting despite nonoptimal reperfusion delays.

The timing of reinfarction may largely explain the benefits of primary PCI in the more recent cohort. One study in a large cohort of acute myocardial infarction patients showed that reinfarction following fibrinolysis occurs at a median of 2.2 days following the index event and is associated with poorer clinical outcomes (13). In the 1999 to 2000 cohort of patients who were successfully treated with fibrinolysis and who underwent a cardiac catheterization during the index hospitalization, catheterization was performed an average of 4.8 days after the index event, which was later than the usual timing of reinfarction. Risk stratification for these patients therefore likely failed to prevent early reinfarction, which may explain the large benefit of primary PCI on this clinical outcome in the more recent cohort.

We observed a two-day reduction in median hospital length of stay during this five-year period. The magnitude of this reduction is similar to previous reports. In the Stenting versus thrombolysis in acute myocardial infarction trial (STAT) (3), a three-day reduction in the median length of stay was observed. In the C-PORT trial (6), a 1.5-day reduction was also observed. Given that 50% of the total costs for an acute myocardial infarction episode are related to length of stay during the index hospitalization (14), our change in reperfusion strategy may have contributed to the reduction of health care expenditures.

Differences in baseline characteristics observed in our population may be explained by several factors. It may reflect temporal trends observed in STEMI patients, in which age at presentation has increased in recent years, as shown by Masoudi et al (15). With improvements in the management of acute STEMI and the postinfarct period, survival has gradually improved and may have contributed to an 'older' pool of patients at risk for myocardial infarction. Also, primary PCI may have been offered to older patients who were not eligible for fibrinolysis. Unfortunately, this hypothesis cannot be verified because data on nonreperused patients are not available. However,

TABLE 4
Clinical in-hospital outcomes

Outcome	1999 to 2000 cohort* (n=114)	2004 to 2005 cohort† (n=129)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	P for adjusted OR
Death, reinfarction or any stroke, n (%)	25 (21.9)	20 (15.5)	0.65 (0.34–1.25)	0.46 (0.21–1.02)	0.055
Death	14 (12.3)	14 (10.9)	0.87 (0.40–1.91)	0.67 (0.25–1.79)	0.422
Reinfarction	12 (10.5)	4 (3.1)	0.27 (0.09–0.87)	0.28 (0.08–0.95)	0.041
Any stroke	2 (1.8)	3 (2.3)	1.33 (0.22–8.12)	1.09 (0.14–8.87)	0.934
TIMI major bleeding, n (%)	10 (8.8)	8 (6.2)	0.69 (0.26–1.81)	0.67 (0.21–2.10)	0.488

*Period from July 1999 to June 2000; †Period from April 2004 to March 2005. TIMI Thrombolysis In Myocardial Infarction

the five-year difference observed between the two cohorts should have disadvantaged the 2004 to 2005 cohort. Diagnosis of hypertension and dyslipidemia were also drastically different. This may be the result of higher recognition by treating physicians because early detection and treatment of vascular risk factors have been emphasized in recent years. We cannot exclude that data abstraction may have had a role in such differences in hypertension and dyslipidemia, but the marked difference in age is not likely to be due to such factors.

The main message of our study is that the benefits of a change in reperfusion strategy in favour of mechanical reperfusion were observed in a large nonselected population despite door-to-reperfusion delays that were longer than ideal. Only 23.4% of our patients received primary PCI in a timely fashion, according to published guidelines (9). The ideal door-to-reperfusion delay in STEMI has generated great debates in recent years. In fact, a recent meta-analysis of published RCTs demonstrated that the benefit of primary PCI over fibrinolysis on 30-day mortality was present despite PCI-related delay of up to 120 min (16). Also, a large Swedish registry of STEMI (17) demonstrated a survival advantage with primary PCI over fibrinolysis, with even greater PCI-related delays. However, these reports (16-17) all emphasized the importance of reducing time-to-reperfusion delays to improve hard clinical outcomes such as death. In our institution, we have been applying some of the recommendations presented by Bradley et al (18), but this is obviously insufficient. One recently published registry (11) that studied time to reperfusion in 17 Quebec hospitals, including our centre, reported median door-to-balloon times of 109 min in patients who presented to a primary PCI hospital. Improving reperfusion times requires interventions at every step in the early management of STEMI, from emergency medical services to the operator in the catheterization laboratory (19).

Limitations

The present study has several limitations that need to be acknowledged. First, a retrospective cohort design with historical controls has limited value to address the impact of a treatment strategy because of the significant number of imbalanced cofactors. However, as presented earlier, the recent cohort was older and had more documented hypertension, although it had more favourable outcomes. Nevertheless, the effect of other cotreatment strategies such as a higher use of acetylsalicylic acid, statins or angiotensin-converting enzyme inhibitors could have favoured better outcomes in this group, although one would not expect that it would largely explain the difference in very short-term in-hospital

outcomes. A recent meta-analysis by Hultén et al (20) showed no impact on cardiovascular events at one month of early intensive statin therapy for acute coronary syndromes. The benefits of intensive statin therapy appeared four to six months after the initial event. Unfortunately, details for such medications were not available to clarify this limitation. Second, the small sample size limited our ability to assess the impact of the reperfusion strategy in many of the individual outcomes measured, including stroke. Such limitation also restricted us in performing subgroup analysis or stratification of patients according to presentation delays. A higher proportion of very early presenters could also have worked in favour of the recent cohort. However, the composite of in-hospital death, reinfarction or stroke among early presenters (2 h or less) was 18.4% for the 1999 to 2000 cohort and 14.5% for the 2004 to 2005 cohort. Selection bias could have been introduced in the decision regarding whether to use a reperfusion strategy in some patients. Data on patients who did not receive any reperfusion strategy were not available to help clarify this important limitation. However, such bias would have disfavoured the more recent cohort, given that it is likely that primary PCI was used more often in sicker patients compared with fibrinolysis therapy in the 1999 to 2000 cohort. However, we studied consecutive patients to minimize this bias. Despite these limitations, our results are in accordance with the published literature of RCTs on reperfusion strategies and they should only be used to validate the application of a primary PCI strategy in a real-life context.

CONCLUSION

Our study showed that a change in the preferred reperfusion strategy for STEMI toward exclusive primary PCI with an aggressive antiplatelet therapy was associated with an adjusted 54% reduction in the combined in-hospital death, reinfarction or stroke rate in a nonselected population, despite door-to-reperfusion delays that were longer than ideal. The improvement observed in this outcome was largely driven by a strong reduction in reinfarction rate. We also observed a two-day reduction in hospital length of stay. Finally, continuous and more vigorous efforts are needed to reduce reperfusion delays to further improve hard clinical outcomes.

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