Original Article

Pharmacoinvasive Strategy vs Primary Percutaneous Coronary Intervention in Patients With ST-Elevation Myocardial Infarction: Results From a Study in Mexico City

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ABSTRACT

Background: A low proportion of patients with ST-elevation myocardial infarction (STEMI) in low- to middle-income countries receive reperfusion therapy. Although primary percutaneous coronary intervention (PCI) is the method of choice, a pharmacoinvasive strategy (PIs) is reasonable when primary PCI cannot be delivered on a timely basis. The aim of our study was to assess the efficacy and safety of a PIs compared with primary PCI in a real-world setting.

RÉSUMÉ

Contexte : Une faible proportion des patients qui subissent un infarctus du myocarde avec élévation du segment ST (STEMI) dans les pays à revenus faibles/intermédiaires reçoivent un traitement de reperfusion. Même si l'intervention coronarienne percutanée (ICP) primaire constitue la méthode de prédilection, une stratégie pharmaco-invasive représente une option raisonnable lorsque l'ICP primaire ne peut être réalisée dans un délai acceptable. Cette étude

In patients with ST-elevation myocardial infarction (STEMI), timely reperfusion is of paramount importance. The choice between primary percutaneous coronary intervention (pPCI) or intravenous fibrinolytic agents depends on the time to effective treatment delivery, availability, and total ischemic time.[1] Although pPCI is the preferred strategy according to clinical guidelines,[2-4] limited resources, the lack of infrastructure, and challenges to achieve timely pPCI have fostered

patients to receive significantly less reperfusion therapies in low- to middle-income countries (LMICs).[3,4]

Although significant barriers for timely reperfusion in patients with STEMI are frequently present in LMICs, previous experiences have shown that the implementation of regional STEMI systems of care might lead to higher use of evidence-based therapies and lower mortality.[5,6] The pharmacoinvasive strategy (PIs) is on the basis of the widespread availability of fibrinolysis and the relative simplicity of its administration to restore myocardial blood flow totally or partially, coupled with cardiac catheterization and clinically appropriate percutaneous coronary intervention (PCI) delivered urgently for patients with failure to reperfuse, or scheduled in those with successful reperfusion. Randomized clinical trials[7,8] and observational studies[9,10] have shown a similar efficacy and safety of a PIs compared with pPCI, and a PIs is considered a reasonable alternative when pPCI cannot be delivered on a timely basis.[11] However, evidence from patients with STEMI who

Methods: This was a prospective registry that included patients with STEMI who received reperfusion during the first 12 hours from symptom onset. The primary composite end point was the occurrence of cardiovascular death, cardiogenic shock, recurrent myocardial infarction, or congestive heart failure at 30 days according to the reperfusion strategy used. The key safety end point was major bleeding (Bleeding Academic Research Consortium [BARC] score 3-5) at 30 days.

Results: We included 579 patients with STEMI, 49.7% underwent primary PCI and 50.2% received PIs. Those who received a PIs approach were more likely to present with Killip class > 1 and to have a history of diabetes but were less likely to have a previous cardiovascular disease diagnosis. No statistically significant difference was shown in the primary composite end point according to reperfusion strategy (hazard ratio for PIs, 0.76; 95% confidence interval, 0.48-1.21; $P = 0.24$). Major bleeding was not different among groups (hazard ratio for PIs, 0.92; 95% confidence interval, 0.45-1.86; $P = 0.81$). Two patients in the PIs group (0.6%) and no patients in the PCI group had intracranial bleeding ($P = 0.15$).

Conclusions: In this prospective real-world registry, major cardiovascular outcomes and bleeding were not different among patients who underwent a PIs or primary PCI. The study suggests that a PIs is an effective and safe option for patients with STEMI when access to primary PCI is limited.

visait à évaluer l'efficacité et l'innocuité d'une stratégie pharmaco-invasive comparativement à une ICP primaire dans la pratique courante.

Méthodologie : Cette étude consistait en une étude de registre prospective et regroupait des patients présentant un STEMI et ayant subi une reperfusion pendant les 12 heures suivant l'apparition des symptômes. Le principal critère d'évaluation regroupé correspondait à l'occurrence du décès cardiovasculaire, du choc cardiogénique, d'une récidive de l'infarctus du myocarde ou d'une insuffisance cardiaque congestive dans les 30 jours suivants, selon la stratégie de reperfusion utilisée. Le principal critère d'évaluation de l'innocuité était les hémorragies majeures (score de 3 à 5 selon le Bleeding Academic Research Consortium [BARC]) à 30 jours.

Résultats : L'étude regroupait 579 patients présentant un STEMI, dont 49,7 % avaient subi une ICP primaire et 50,2 % avaient reçu une stratégie pharmaco-invasive. Les patients ayant reçu une stratégie pharmaco-invasive étaient plus susceptibles de présenter une classe de Killip > 1 et des antécédents de diabète, mais étaient moins susceptibles d'avoir déjà reçu un diagnostic de maladie cardiovasculaire. Aucune différence significative sur le plan statistique n'a été observée pour ce qui est du principal critère d'évaluation regroupé selon la stratégie de reperfusion (rapport des risques instantanés [RRI] de la stratégie pharmaco-invasive : 0,76; intervalle de confiance [IC] à 95 % : 0,48-1,21; $p = 0,24$). Aucune différence n'a été observée entre les groupes quant aux hémorragies majeures (RRI de la stratégie pharmaco-invasive : 0,92; IC à 95 % : 0,45-1,86; $p = 0,81$). Deux patients du groupe ayant reçu une stratégie pharmaco-invasive (0,6 %) ont présenté une hémorragie intracrânienne, comparativement à aucun patient du groupe ayant subi une ICP ($p = 0,15$).

Conclusions : Selon cette étude de registre prospective en pratique courante, les résultats concernant les hémorragies et les événements cardiovasculaires majeurs n'ont pas été différents entre les patients ayant subi une ICP primaire et ceux ayant reçu une stratégie pharmaco-invasive. L'étude suggère que la stratégie pharmaco-invasive constitue une option sûre et efficace pour les patients qui présentent un STEMI, lorsque l'accès à une ICP primaire est limité.

underwent a PIs or pPCI in LMICs is still scarce. Our aim was to assess the efficacy and safety of a PIs compared with pPCI in a real-world setting among patients with STEMI in a large metropolitan area from a LMIC.

Methods

Study design and population

The PHASE-MX (Evaluation of **Pha**rmacoinvasive Strategy versus percutaneous coronary intervention in patients with acute myocardial infarction with **S**T-segment **E**levation at the National Institute of Cardiology in M**éx**ico City) study was a prospective registry that included patients with STEMI and who presented at Mexico City's STEMI Network (ClinicalTrials.gov identifier NCT03974581). Details of the study design have been previously published.[12] In brief, the study included consecutive patients aged 18-99 years old with the diagnosis of STEMI from Mexico City's STEMI Network, who received either a PIs or pPCI during the first 12 hours from symptom onset. The study was conducted according to the principles of the Declaration of Helsinki, approved by the local

research and ethics committees, and all participants provided informed consent for inclusion in the study.

Settings

The Mexico City STEMI Network comprises 60 hospitals within a densely populated metropolitan area, located around a large-volume main PCI hub (Fig. 1). This network offers health care services for patients without social security, within the lowest socioeconomic tercile. Although there are several catheterization laboratories in Mexico City, all of the angiographies and PCIs (primary and pharmacoinvasive) in our study were performed at the study centre, which is the only third-level cardiovascular specialty hospital with a cardiac catheterization laboratory available 24/7 within the network. The median transfer distance from peripheral hospitals to the PCI hub is 25.2 km. Moreover, Mexico City has a population density of 5966 inhabitants per kilometer squared and heavy traffic conditions during some hours of the day. Further information regarding the high partition of the health care services and STEMI care in Mexico are reported elsewhere.[13]

Araiza-Garaygordobil et al.
Pharmacoinvasive Strategy in México City

411

Procedures

The network's treatment algorithm recommended pPCI if the procedure could be performed in < 120 minutes since the diagnosis and the anticipated time interval from the transfer of the patient from a non-PCI centre to a PCI centre to be less than 60 minutes. A PIs comprising fibrinolysis at the first medical contact centre (at 1 of the 60 hospitals in the STEMI network) and subsequent PCI (elective in cases of successful fibrinolysis and emergent in cases of failed fibrinolysis) was recommended for the rest of the patients.

In patients who underwent a PIs, the choice of fibrinolytic agent depended on the availability in each hospital, and included tenecteplase, alteplase, and streptokinase; all fibrinolysis infusions occurred in hospital settings, because prehospital fibrinolysis is not available within the network. Successful fibrinolysis and the need for rescue intervention was assessed in the first 90 minutes after the administration of the fibrinolytic agent by the on-site treating physician. If there was < 50% ST-segment elevation resolution on the worst lead and persistence of severe chest pain, a rescue intervention was deemed to be needed and the patient shipped as quickly as possible to the PCI centre. Communication between non-PCI centres and the study centre was made via telephone; post lysis patients were transported as soon as an intensive care unit bed was available at the PCI centre. The decision on to whom to offer lysis or transfer for PCI rested with the attending physician in charge of the case, with real-time communication with the study centre. Urgent angiography was performed when hemodynamic instability, refractory ventricular arrhythmias, ongoing chest pain, or recurrent ST-segment elevation occurred. In patients in whom cardiogenic shock was present at the first medical evaluation, pPCI was recommended as the reperfusion strategy; inotropes, vasopressors, intra aortic balloon pump placement, and other therapies were used according to the treating physician criteria. Patients with successful reperfusion by fibrinolytic agents were scheduled routinely for nonurgent cardiac catheterization, ideally within the first 24 hours after hospital admission. Regardless of the chosen reperfusion strategy, all patients included in the present study were finally transferred to the study centre and underwent coronary angiography with or without PCI as appropriate. The study procedures are depicted in Supplemental Figure S1.

Data collection

Data on baseline characteristics, treatment intervals, reperfusion therapy, hospital management, and in-hospital clinical events were collected by 2 of the investigators using digital standardized case report forms. We excluded patients with more than 12 hours of total ischemic time (> 12 hours from symptom onset to treatment), unknown ischemic time, those who did not receive acute reperfusion, with in-hospital STEMI, or with a discharge diagnosis other than STEMI. For analytical purposes of the study, a PIs was considered as patients who initially underwent fibrinolysis followed by either routine subsequent PCI or rescue PCI, and pPCI was considered as those who initially underwent PCI.

Study end points

The primary composite end point included the occurrence of cardiovascular death, cardiogenic shock, recurrent myocardial infarction (MI), or congestive heart failure at 30 days of follow-up; the key safety end points included the proportion of patients with major bleeding (Bleeding Academic Research Consortium [BARC] score 3-5) at 30-day follow-up and the proportion of patients with intracranial hemorrhage. To assess for possible heterogeneity in the treatment effect according to the site of first medical contact, we conducted a secondary analysis excluding all patients with
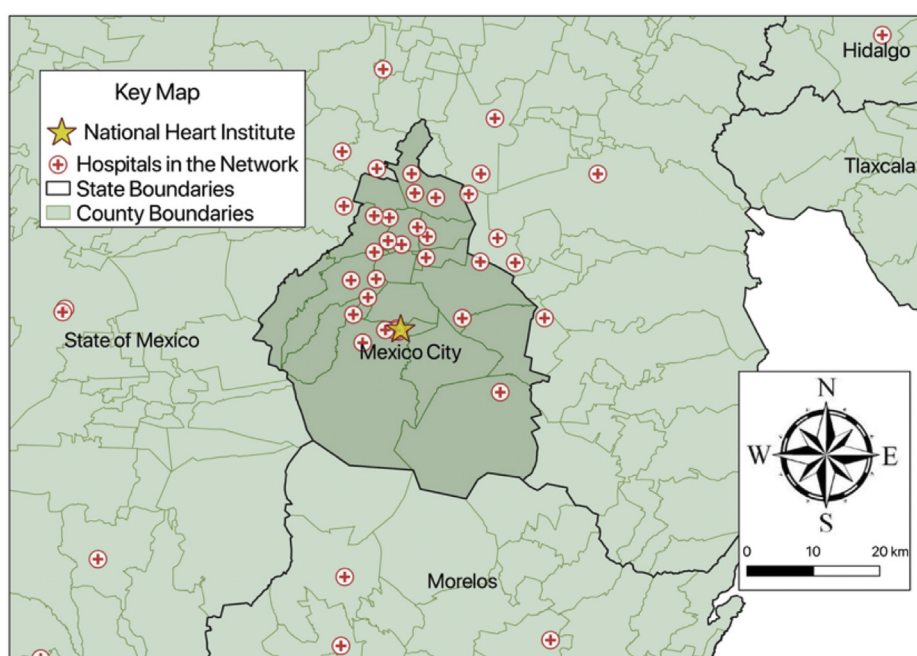

Figure 1. Map of the hospitals included in the Mexico City STEMI Network.

a first medical contact at the study centre. Secondary objectives included the time to first occurrence of each component of the primary composite end point.

Two of the authors, blinded to reperfusion treatment, adjudicated the outcomes. In case of discordance, a third blinded author issued the final opinion. Patients were scheduled for a telephone call on day 30 after the index event; if deemed necessary, on-site visit was planned for further evaluation. Outcomes were on the basis of international standardized definitions for end points in clinical trials.[14] Periprocedural MI was not included as part of the definition of recurrent MI. Cardiogenic shock was considered as an event if it persisted > 24 hours after hospital admission.

Statistical analysis and sample size calculation

We described and compared quantitative variables depending on their distribution according to reperfusion strategy (PIs vs pPCI). Normally distributed variables, evaluated using the Shapiro-Wilk test, were reported as means and standard deviations and compared with Student t test. Nonnormally distributed variables were reported with medians and interquartile ranges and compared with Mann-Whitney test. Categorical variables were described with frequencies and percentages and compared using χ^2 test or Fisher exact test.

Initially, we estimated the sample size accounting for statistical power (1 β) of 80%, and an α level of 0.05, estimating the primary composite end point rate at 30 days, to be 12.4% in patients who underwent a PIs and 14.3% in patients who underwent pPCI, with a maximum tolerated difference of 8% between groups, and accounting for a loss to follow-up of 10%.[5] A total sample size of 326 patients was estimated. However, after 12 months of recruitment, the steering committee suggested a protocol amendment to augment sample size to increase power (1 β = 90%). The final estimated sample size comprised 496 patients (248 per arm).

For the analysis of the primary end point, we calculated the differences in the time to the first event of the composite outcome for each group, using Log rank test and depicted using Kaplan-Meier curves. Additionally, we used a Cox regression model to compare the effectiveness of the PIs compared with primary PCI. We evaluated the proportional hazard assumption with the Schoenfeld residual test and checked for linear assumption with residual plots. In secondary analyses, we used univariate Cox regression models to assess the association between clinically relevant covariates and the composite outcome. From these univariate models, we selected the variables that were statistically significant and included in an adjusted model.

Because the underlying differences between participants who received PCI vs a PIs could bias our findings, we used propensity score matching. The propensity scores were estimated for the likelihood of undergoing a PIs using a multiple logistic regression model that contained the following clinically meaningful variables selected by the investigators: age, sex, diabetes, hypertension, dyslipidemia, smoking history, chronic kidney disease, previous MI, previous PCI, atrial fibrillation, vital signs on arrival, N-terminal pro brain natriuretic peptide (NTproBNP) on arrival, total ischemic time, and MI localization. Matching was performed using a greedy matching protocol (1:1 nearest neighbour matching, without replacement) with a caliper width of 0.2 of the SD. Matched patients were further analyzed for the occurrence of the primary end point using Cox proportional hazards regression. We used STATA version 14.1 (StataCorp LP, College Station, TX) for all statistical analyses.

Results

Patient population

From April 2018 to February 2020, 617 patients with STEMI were consecutively treated, and 38 were excluded (Fig. 2). In the final population (n = 579), 288 patients
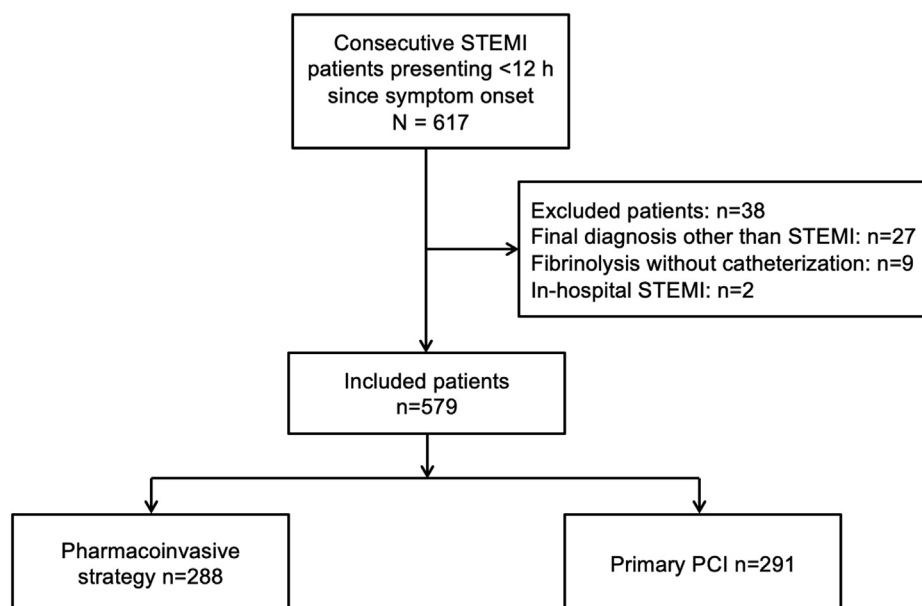

Figure 2. Study flow chart. PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

Araiza-Garaygordobil et al.
Pharmacoinvasive Strategy in México City

413

Table 1. Baseline characteristics according to administered reperfusion strategy.

Characteristic	Primary PCI (n = 288)	Pharmacoinvasive strategy (n = 291)	P
Age, years	59.7 (10.8)	57.3 (10.9)	0.56
Female sex, n (%)	250 (12.8)	250 (13.1)	0.83
Clinical presentation			
Heart rate (IQR), beats per minute	81.5 (67-90)	80.21 (70-90)	0.50
Systolic blood pressure (IQR), mm Hg	136 (117-150)	132 (110-150)	0.3
Diastolic blood pressure (IQR), mm Hg	83.9 (70-96)	77.9 (70-86)	0.07
Infarct location, n (%)			
Anterior	120 (42.0)	123 (42.2)	0.82
Inferior/lateral	161 (55.9)	152 (52.2)	
Other	7 (0.02)	16 (0.05)	
Killip-Kimball class I, n (%)	180 (61.8)	124 (45.5)	0.001
Cardiogenic shock on admission, n (%)	10 (3.4)	9 (3.0)	0.79
GRACE upon admission	120.5 (98-143)	123 (100-149)	0.24
CRUSADE upon admission	26 (18-37)	28 (19-35)	0.49
Comorbidities, n (%)			
Hypertension	136 (47.2)	125 (42.9)	0.3
Diabetes mellitus	90 (31.2)	118 (40.6)	0.01
Hypercholesterolemia	64 (22.2)	50 (17.2)	0.13
Current smoker	118 (40.9)	136 (46.7)	0.17
Obesity	61 (21.1)	72 (24.7)	0.31
Chronic kidney disease	5 (1.7)	6 (2.0)	0.77
Medical history, n (%)			
Myocardial infarction	36 (12.5)	21 (7.2)	0.06
Coronary bypass graft	7 (2.4)	1 (0.3)	0.07
Previous PCI	27 (9.3)	12 (4.1)	0.03
Known heart failure	4 (1.3)	0	0.053
Atrial fibrillation	2 (0.6)	0	0.26

CRUSADE, **C**an **R**apid risk Stratification of **U**nstable angina patients **S**uppress **AD**verse outcomes with **E**arly Implementation of the ACC/AHA guidelines Bleeding Score; GRACE, Global Registry of Acute Coronary Events, IQR, interquartile range; PCI, percutaneous coronary intervention.

(49.7%) underwent pPCI, and 291 (50.2%) received a PIs. Most patients were male (86.3%), the mean age was 58.5 ± 10.9 years, 35.9% had diabetes, 45.0% had hypertension, and 19.6% had hypercholesterolemia. Table 1 shows baseline characteristics sorted according to the reperfusion strategy used.

Table 2. In-hospital medications, transfer distance, and time delays according to administered reperfusion strategy

	Primary PCI (n = 288)	Pharmacoinvasive strategy (n = 291)	P
In-hospital medications, n (%)			
Aspirin	276 (95.8)	286 (98.2)	0.32
P2Y12i; clopidogrel	224 (77.7)	268 (92.0)	0.02
P2Y12i; prasugrel/ticagrelor	54 (18.7)	9 (0.03)	0.001
Anticoagulant	288 (100)	280 (96.0)	0.9
Statin	280 (97.2)	274 (94.1)	0.78
β-Blocker	219 (76.0)	210 (72.1)	0.56
ACEI/ARB	224 (77.7)	238 (81.7)	0.88
Fibrinolytic agent			
Tenecteplase		221 (77.0)	
Alteplase		63 (21.9)	
Streptokinase		3 (1.0)	
Transfer distance and time delays			
Symptom onset to first medical contact (IQR), min	120 (60-270)	117 (60-227)	0.82
Total ischemia time, min, IQR	320 (205-525)	325 (180-587)	0.73
Patients with ischemic time > 6 h, n (%)	110 (43.1%)	116 (46.7)	0.41
Door to balloon/door to needle time, min	70 (60-98)	40 (10-117)	
First medical contact to balloon/needle (IQR), min	132 (80-245)	120 (59-237)	
Time to routine angiography, h		22.0 (6.0-48.0)	
Time to rescue angiography, h		10.8 (4.3-24.0)	
Distance from first medical contact to PCI-capable hospital, km	21 (1.3-67.7)	20.8 (1.3-29.1)	0.43

ACEI/ARB: angiotensin converting enzyme inhibitors/angiotensin receptor blockers; IQR, interquartile range; PCI, percutaneous coronary intervention; P2Y12i, P2Y12 inhibitors.
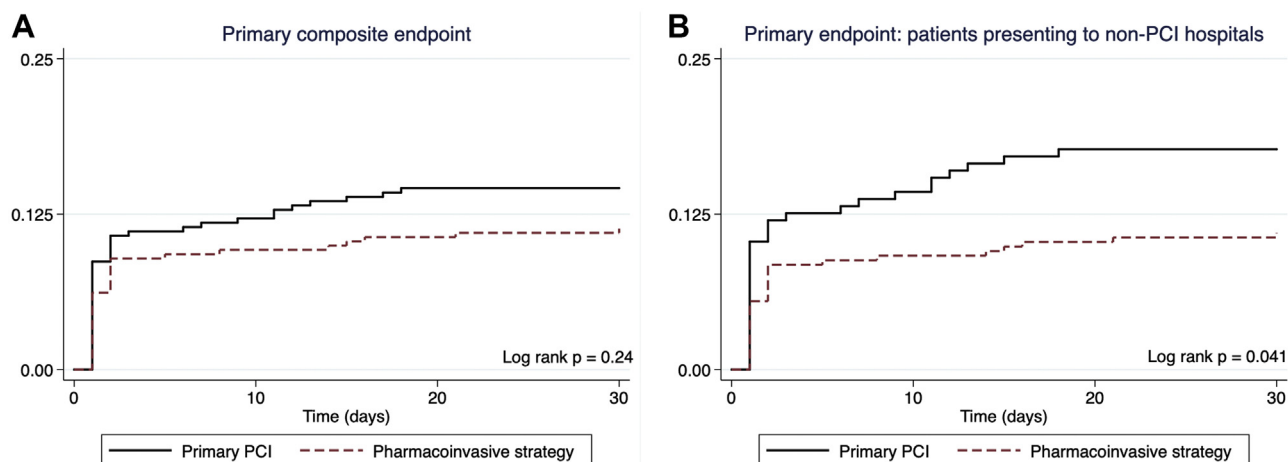
Figure 3. Kaplan-Meier curves of the primary composite end point of cardiovascular death, cardiogenic shock, recurrent myocardial infarction, or congestive heart failure at 30-day follow-up. (A) Results of the whole cohort. (B) Results among the group of patients who had first medical contact outside the study centre. PCI, percutaneous coronary intervention.

Reperfusion therapy

Table 2 shows in-hospital medications and treatment delays according to the reperfusion strategy used. Tenecteplase was the most frequent fibrinolytic agent (77.0%). All patients received subsequent coronary angiography. Fibrinolysis was successful in 171 (59.1%) of patients treated with a PIs and the rest received rescue PCI. The median time from successful fibrinolysis to nonurgent cardiac angiography was 22.5 (interquartile range, 6.0-48.0) hours. The median time from failed fibrinolysis to rescue PCI was 10.8 (interquartile range, 4.3-24) hours. In the pPCI group 89.5% received stent angioplasty, 6.2% received plain old balloon angioplasty (POBA), 3.1% received only intravenous glycoprotein-IIb/IIIa inhibitors (mainly due to coronary artery ectasia) and 2 patients were scheduled for emergency coronary artery bypass grafting (CABG). In the pPCI group, 89.5% of patients received stent angioplasty, 6.2% received POBA, 3.1% received only intravenous glycoprotein-IIb/IIIa inhibitors (mainly due to coronary artery ectasia), and 0.06% of the patients were scheduled for emergency CABG. In the PIs group, 88.3% received stent angioplasty, 3.1% received POBA, and 2.1% were scheduled for emergency CABG.

Among patients who underwent pPCI, 112 (39.0%) had a first medical contact at the study centre, and 175 (60.9%) at other centres, with a median transfer distance of 21 (range, 1.3-67.7) km. Among patients who underwent a PIs, 12 (4.2%) had a first medical contact in the study centre, and 273 (95.7%) at one of the hospitals from the STEMI network, with a median transfer distance of 20.8 (range, 1.3-29.1) km. Only 32 patients (11.0%) were treated with pPCI with a total ischemic time of less than 120 minutes. Supplemental Figure S2 depicts timelines of each group.

Treatment characteristics according to administered reperfusion therapy

Compared with pPCI, a higher proportion of patients in the PIs group had diabetes (40.6 vs 31.2; $P = 0.01$) and a lower rate of Killip-Kimball I class upon admission (61.8 vs 45.5%; $P = 0.001$). Patients who underwent pPCI received

Table 3. Main efficacy and safety outcomes

	Primary PCI (n = 288)	Pharmacoinvasive strategy (n = 291)	P^*
Efficacy, primary outcome			
Cardiovascular death, cardiogenic shock, recurrent MI, or congestive heart failure	42 (14.5)	33 (11.3)	0.24
Efficacy, components of the primary outcome			
Cardiovascular death	18 (6.2)	14 (4.8)	0.44
Cardiogenic shock	14 (4.8)	13 (4.4)	0.81
Recurrent MI	4 (1.3)	1 (0.3)	0.17
Congestive heart failure	30 (10.4)	21 (7.2)	0.18
Safety			
Major bleeding (BARC 3-5)	17 (5.9)	15 (5.1)	0.69
Intracranial bleeding	0 (0)	2 (0.6)	0.15

Data are presented as n (%) except where otherwise stated.

BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention.

* P value for univariate analysis.

Araiza-Garaygordobil et al.
Pharmacoinvasive Strategy in México City

415

prasugrel/ticagrelor as adjunctive P2Y12 inhibitor therapy more frequently (18.7 vs 0.03%; $P = 0.001$). A high use of evidence-based medications in the acute setting was reported for both groups. There were no other relevant differences in clinical presentation, comorbidities, medical history, use of in-hospital medications, and delays to treatment.

Study outcomes

The primary composite end point of the study occurred in 42 (14.5%) patients who underwent pPCI and in 33 (11.3%) patients who received a PIs. We did not find a statistically significant difference in the time to first occurrence of the composite end point according to reperfusion strategy (hazard ratio [HR] for PIs, 0.76; 95% confidence interval [CI], 0.48-1.21; log rank $P = 0.24$; Fig. 3A). Among the components of the primary outcome, a numerically lower rate of events was shown in the PIs group that did not reach statistical significance (Table 3).

The key safety end point of major bleeding (BARC score 3-5) at 30-day follow-up was not different among groups (HR for PIs, 0.92; 95% CI, 0.45-1.86; $P = 0.81$). Two patients in the PIs group had intracranial bleeding (0.6%; both were receiving streptokinase), and no intracranial bleeding was registered in the pPCI group, with no statistically significant difference ($P = 0.15$).

A secondary analysis to assess the heterogeneity of treatment effect on the basis of the site of first medical contact showed that, among the group of patients who had first medical contact outside the study centre, there was a 40% reduction in the risk of the primary composite end point (HR, 0.60 for PIs; 95% CI, 0.36-0.99; $P = 0.048$) for those who underwent PIs compared with pPCI (Fig. 3B). No statistically significant differences in the rates of the composite end point

were shown in patients who initially presented in non-PCI hospitals vs the study centre (13.6% vs 10.4%; $P = 0.35$).

In univariate analysis, age older than 60 years (HR, 2.27), history of diabetes (HR, 1.57), history of hypertension (HR, 2.1), creatinine on admission > 2.0 mg/dL (HR, 4.68), NTproBNP > 800 pg/mL (HR, 2.98), C-reactive protein > 6.0 pg/mL (HR, 1.55), serum glucose > 160 mg/dL (HR, 2.78), heart rate > 80 beats per minute (HR, 1.86), and site of first medical contact (PCI hub vs non-PCI hub HR, 0.60) were significantly associated with the primary outcome. In the multivariate adjusted analysis, the statistically significant associations with the composite outcome persisted for age older than 60 years (HR, 1.67), admission creatinine > 2.0 mg/dL (HR, 2.30), NTproBNP (HR, 1.99), glucose > 160 mg/dL (HR, 2.46), and admission heart rate > 80 beats per minute (HR, 1.63). The association between reperfusion strategy or the site of first medical contact and the primary outcome was not statistically significant (Table 4).

Finally, in 242 patients matched according to propensity scores (121 pPCI, 121 PIs), we showed similar results—the risk of the primary end point in the matched cohort for patients who underwent a PIs was not statistically different from those who underwent pPCI (HR for PIs, 1.00; 95% CI, 0.46-2.15; $P = 0.99$). Baseline characteristics of matched patients, according to reperfusion strategy used, is included in Supplemental Table S1.

Discussion

In this real-world registry of STEMI patients from a large metropolitan network in a middle-income country, outcomes of a PIs and pPCI were similar regarding major adverse cardiac events and major bleeding. Additionally, a lower rate of

Table 4. Univariate and multivariate analysis

Variable	Model 1 (crude)		Model 2 (multivariable adjusted)	
	HR (95% CI)	P	HR (95% CI)	P
Reperfusion strategy (reference: pPCI)	0.70 (0.41-1.20)	0.20	0.75 (0.45 - 1.22)	0.25
Male sex	0.62 (0.31-1.23)	0.17		
Age older than 60 years	**2.27 (1.41-3.65)**	**0.001**	**1.67 (1.19 - 2.75)**	**0.042**
Diabetes	**1.57 (1.00-2.48)**	**0.049**	0.68 (0.40 - 1.16)	0.16
Hypertension	**2.10 (1.32-3.36)**	**0.002**	1.53 (0.92 - 2.54)	0.095
Chronic kidney disease	0.8 (0.11-5.8)	0.83		
"Successful" fibrinolysis	0.85 (0.38-1.92)	0.71		
Creatinine > 2.0 mg/dL	**4.68 (2.92-7.51)**	**< 0.001**	**2.30 (1.36 - 3.91)**	**0.002**
Initial NTproBNP > 800 pg/mL	**2.98 (1.7-5.0)**	**< 0.001**	**1.99 (1.14 - 3.48)**	**0.015**
C-reactive protein > 6.2 pg/mL	1.55 (0.96-2.50)	0.069		
Glucose > 160 mg/dL	**2.78 (1.67-4.65)**	**< 0.001**	**2.46 (1.38 - 4.38)**	**0.002**
Heart rate > 80 beats per minute	**1.83 (1.15-2.91)**	**0.01**	**1.63 (1.01 - 2.63)**	**0.042**
Systolic blood pressure less than median	0.60 (0.33-1.11)	0.10		
Diastolic blood pressure < 80 mm Hg	**1.90 (1.19-3.04)**	**0.007**	1.70 (1.05 - 2.74)	0.08
Killip-Kimball class > 1	0.75 (0.25-2.23)	0.60		
Site of first medical contact (non-PCI hub)	0.76 (0.42-1.39)	0.38		

Bold values represent statistically significant associations.

Variables associated with the occurrence of the composite end point of cardiovascular death, cardiogenic shock, recurrent MI, or stroke. Model 1: each line represents a separate Cox model. Model 2: model including all variables that were statistically significant in univariable models (from model 1). Only variables with a significant association were inputted in the multivariate analysis.

CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; NTproBNP, N-terminal pro brain natriuretic peptide; PCI, percutaneous coronary intervention; pPCI, primary percutaneous coronary intervention.

cardiovascular events was shown in patients who underwent a PIs when first medical contact happened in a non-PCI hub.

The outcomes of STEMI patients have improved during the past decades, mostly because of coronary reperfusion.[15] Guidelines provide a class I, level of evidence A recommendation for reperfusion therapy with either primary PCI or systemic fibrinolysis[3,16,17] during the first 12 hours since symptom onset in patients with STEMI. However, it is noteworthy that access to reperfusion therapy is still limited in several countries, and great heterogeneity in treatment and mortality rates exist.[4] For example, previous studies have reported lower rates of reperfusion therapy in LMICs,[3] where access to either fibrinolytic agents or pPCI might be challenging because of the lack of awareness, severe paucity of resources, and lack of STEMI systems of care.[11] The difficulties for the delivery of timely reperfusion therapy in large metropolitan areas have also been identified.[18,19] Although metropolitan areas tend to have a higher ratio of cardiac catheterization labs per inhabitant, traffic conditions, distances, and overburden of hospitals might lead to delays in reperfusion therapy.[20]

Randomized and observational studies have shown total ischemic times ranging from 100 to 165 minutes for a PIs and 178 to 255 minutes for pPCI.[7,9-10] Our study showed total ischemic times of 325 and 320 minutes for a PIs and pPCI, respectively. Median time from first medical contact to needle was 120 minutes, which might be partially explained by the lack of fibrinolytic agents in all hospitals and the need for hospital transfer in many cases. The relatively late use of fibrinolysis in our study might also contribute to the high proportion of patients with failed fibrinolysis (40.1%) in whom rescue PCI was used. In this regard, previous studies have shown a higher rate of cardiovascular adverse events in patients with failed fibrinolysis compared with those with successful fibrinolysis and who were scheduled for PCI.[21]

The time from fibrinolysis administration to either elective (22.0 hours) or rescue (10.8 hours) angiography in our study, was also markedly longer than in other studies. The **St**rategic **R**eperfusion **E**arly **A**fter **M**yocardial Infarction (STREAM) study[7] showed a median time from fibrinolysis to angiography of 17 hours in elective cases and of 2.2 hours in rescue PCI. The **K**orea **A**cute **M**yocardial **I**nfarction **R**egistry (KAMIR) showed a median time from fibrinolysis to angiography of 41.5 hours, also reflective of true real-world practice.[9] This delay might partially be explained by factors such as the lack of a unified prehospital/ambulance system, the persistent saturation of public hospital systems,[13] and the fact that patients need to wait for the availability of a coronary intensive care unit hospital bed in the PCI centre before they are transferred. Our study highlights the imminent need to accelerate the process of transfer for rescue PCI in cases in which fibrinolysis has failed. Other STEMI systems of care have shown that patients who receive fibrinolysis in the prehospital setting (ambulances) might have shorter times to rescue PCI.[21] It is important to note that our study included patients beyond the first 6 hours of total ischemia time, and previous studies excluded patients with prolonged ischemic times[7]; this fact might add relevance to the current findings,

accounting for the well recognized delays in medical access for STEMI in LMICs.[3]

When we analyzed the results of patients whose first medical contact occurred in a non-PCI centre, a statistically significant reduction in the risk of the primary outcome was observed in the group of patients who underwent a PIs, which might support the use of a PIs whenever pPCI cannot be delivered within guideline-recommended timelines. It is worth emphasizing that all fibrinolytic agents were administered in hospital settings, because prehospital fibrinolysis is not available in the region. In a subanalysis from the STREAM study the outcomes among patients randomized in community hospitals vs prehospital settings were compared, and showed no differences in outcomes irrespective of a successful PIs vs primary PCI[22]; however, patients with failed fibrinolysis were less likely to receive rescue therapy, which might be in line with the finding of prolonged time (10.8 hours) for rescue PCI.

Our results are relevant for national practice, because STEMI 30-day mortality in Mexican patients has been reported as high as 27%,[23] the highest among the Organization for Economic Co-operation and Development countries, and reperfusion rates have been reported as low as 52.6%.[24] A recent white paper positions a PIs as a uniquely attractive option for patients in LMICs, because access to pPCI is limited and infrequently achieved within the guideline-mandated times.[11] In the present study, only 11.0% of the patients from the pPCI group were treated within the guideline-mandated timelines (< 120 minutes),[3] which suggests that a PIs might be a solid option to improve outcomes in the remaining 89% of patients who cannot access timely pPCI.

The 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology guidelines recognize the challenge that Canada's geography represents for timely delivery of myocardial reperfusion in patients with STEMI, and emphasize the need for prompt therapy irrespective of where the patient is initially identified (in the field, at a non-PCI capable centre, or at a PCI-capable centre)[16]; this recommendation should be extrapolated to several LMICs, where pPCI might not be readily available because of a myriad of reasons.

This study has limitations, including the potential selection bias, because only the patients who were transferred to or had their first medical contact at the study centre were included. A possible explanation for the high rate of failed fibrinolysis and rescue PCI might be the potential exclusion of low-risk patients who responded favourably to fibrinolysis and were not transferred for subsequent PCI to the study centres. Similarly, potentially sicker patients or patients who immediately died after STEMI diagnosis in first medical contact might have not been recruited. However, we performed a secondary analysis in propensity score-matched patients, which yielded the same finding, thus reducing the likelihood that that selection or residual confounding drove our findings. Ischemic and treatment delays were prospectively documented, but in patients who presented to a hospital other than the study centre, time was documented using reference documentation and could be subject to recall bias. The observational nature of the study

Araiza-Garaygordobil et al.
Pharmacoinvasive Strategy in México City

417

might be prone to the omission of unmeasured confounders that could have affected the decision to use either pPCI or a PIs in specific patients; the use of propensity score matching might aid in overcoming this potential bias. Finally, the fact that patients were finally treated in a large tertiary cardiovascular centre might limit the external validity of the results.

In conclusion, in this prospective STEMI real-world registry, major adverse cardiovascular outcomes and major bleeding were not different among patients who underwent a PIs or pPCI. The study suggests that a PIs is a feasible, effective, and safe therapeutic option for patients with STEMI particularly in patients who present to non-PCI hubs. Our results could favour the development of STEMI care systems that use the PIs as a form of effective and safe reperfusion option in areas where access to pPCI is limited.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2020.11.012.