Primary Percutaneous Coronary Intervention Versus In-Hospital Thrombolysis as Reperfusion Therapy in Early-Arriving Low-Risk STEMI Patients

Yaniv Levi MD[1], Aaron Frimerman MD[1], Avraham Shotan MD[1], Michael Shochat MD PhD[1], David S. Blondheim MD[1], Amit Segev MD[2], Ilan Goldenerg MD[2,3], Mark Kazatsker MD[1], Liubov Vasilenko MD[1], Nir Shlomo PhD[3] and Simcha R Meisel MD MSc[1]

[1]Heart Institute, Hillel Yaffe Medical Center, Hadera, Israel
[2]Heart Institute and [3]IACT-Israeli Association for Cardiovascular Trials, Leviev Heart Center, Sheba Medical Center, Tel Hashomer, Israel

ABSTRACT: **Background:** Trials have shown superiority of primary percutaneous intervention (PPCI) over in-hospital thrombolysis in ST-elevation myocardial infarction (STEMI) patients treated within 12 hours of symptom onset. These studies also included high-risk patients, not all of whom underwent a therapeutic intervention.

Objectives: To compare the outcomes of early-arriving stable STEMI patients treated by thrombolysis with or without coronary angiography to the outcomes of PPCI-treated STEMI patients.

Methods: Based on six biannual Acute Coronary Syndrome Israeli Surveys comprising 5474 STEMI patients, we analyzed the outcome of 1464 hemodynamically stable STEMI patients treated within 3 hours of onset. Of these, 899 patients underwent PPCI, 383 received in-hospital thrombolysis followed by angiography (TFA), and 182 were treated by thrombolysis only.

Results: Median time intervals from symptom onset to admission were similar while door-to-reperfusion intervals were 63, 45 and 52.5 minutes for PPCI, TFA and thrombolysis only, respectively ($P < 0.001$). The 30-day composite endpoint of death, post-infarction angina and myocardial infarction occurred in 77 patients of the PPCI group (8.6%), 64 treated by TFA (16.7%), and 36 patients of the thrombolysis only group (19.8%, $P < 0.001$), with differences mostly due to post-infarction angina. One-year mortality rate was 27 (3%), 13 (3.4%) and 11 (6.1%) for PPCI, TFA and thrombolysis-only, respectively ($P = 0.12$).

Conclusions: PPCI was superior to thrombolysis in early-arriving stable STEMI patients with regard to a 30-day composite endpoint driven by a decreased incidence of post-infarction angina. No 1 year survival benefit for PPCI over thrombolysis was observed in early-arriving stable STEMI patients.

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KEY WORDS: ST-elevation myocardial infarction (STEMI), reperfusion therapy, primary percutaneous coronary intervention, thrombolysis

Randomized trials and meta-analyses evaluating reperfusion strategies in patients presenting with acute ST-elevation myocardial infarction (STEMI) have demonstrated superior results for primary percutaneous coronary intervention (PPCI) versus thrombolysis. PPCI yielded lower rates of all-cause and cardiovascular mortality, non-fatal re-infarction, combined endpoint of death, and reinfarction and disabling stroke [1]. Following these results, the preferred reperfusion treatment for STEMI patients in PCI-capable hospitals has shifted in the last 15 years from thrombolysis to PPCI. Current guidelines even recommend transferring STEMI patients from non-PCI capable hospitals to PCI-capable centers for therapy, if done within the required time limit. Consequently, thrombolysis has gradually become a second-line treatment for STEMI, administered mainly when PPCI cannot be performed [2,3].

Careful assessment of the literature shows that the advantage of PPCI was demonstrated mostly in studies that also included high-risk late-arriving patients [1]. Despite the fact that routine early PCI after thrombolysis has been proven superior to delayed, or ischemia-guided PCI [4,5], many of the thrombolysis-treated STEMI patients included in these trials did not undergo coronary angiography during their index hospitalization [1]. This treatment strategy potentially may have increased the occurrence of recurrent ischemia or reinfarction responsible for the higher rate of combined endpoint in thrombolysis-treated patients. However, when evaluating according to treatment strategy and the outcome of early-arriving low-risk STEMI patients included in these trials, it seems that no significant difference can be demonstrated [6-9]. Actually, several randomized trials and registries suggested that thrombolysis may still be considered an acceptable alternative therapy in early-arriving low-risk STEMI patients [6,8-13]. Hence, there is a need to compare the outcome of low-risk STEMI patients presenting early to PCI-capable hospitals according to reperfusion modality administered.

We therefore analyzed the outcome by the reperfusion therapy used of early-arriving stable STEMI patients enrolled in six consecutive biannual national multicenter registries and report their short- and long-term mortality rate.

PATIENTS AND METHODS

STUDY POPULATION

The Acute Coronary Syndrome Israeli Survey (ACSIS) registry is a national biannual database that includes the clinical data of patients admitted to all intensive coronary care units in Israel with a diagnosis of acute coronary syndrome within a 2 month period during the year of the study. Mortality during the first year after the acute event was assessed for hospital survivors by matching their identification numbers with the Israeli National Population Registry. The original population of the present study comprised patients included in six ACSIS registries between 2000 and 2010. For the current analysis we selected all hemodynamically stable STEMI patients admitted to the intensive care unit or emergency department within 3 hours of symptom onset and who received either thrombolysis or PPCI as reperfusion therapy at the discretion of the attending cardiologist. Exclusion criteria included:

- Admission to the hospital beyond 3 hours from symptom onset
- Systolic blood pressure < 100 mmHg on admission
- Heart rate>100 beats per minute (bpm)
- Killip class > 1 at presentation

Patients signed informed consent for participation in the survey and for late follow-up. The patients included in the study were of one of the three following groups: patients treated by PPCI, patients treated by thrombolysis followed by angiography (TFA) during the index hospitalization, or patients treated by thrombolysis only.

DATA COLLECTION

All data were documented on computerized case record forms by treating physicians. Cardiovascular history, risk factors, medications used during hospitalization and at discharge, in-hospital clinical course, 30 day and 1 year mortality as well as vital status at the end of the follow-up period were recorded for each patient.

Symptom-to-needle interval in the thrombolysis-treated patient was defined as the time elapsed from symptom onset to beginning of intravenous infusion of the thrombolytic agent. The time from symptoms to balloon was defined as the time from symptom onset to the first balloon inflation in the PPCI-treated patients.

STATISTICAL ANALYSIS

Baseline characteristics including risk factors, clinical characteristics, laboratory values and hospital course of the three pre-specified reperfusion patient groups (PPCI, TFA, and thrombolysis only) were compared by ANOVA for continuous variables, with PPCI specifically compared to TFA, or by the chi-square test for categorical variables as appropriate. The Kruskal–Wallis ANOVA test was used to compare non-normal variables.

Survival curves were generated for follow-up periods of 5 and 10 years, with groups compared using the Kaplan–Meier long-range test. An early exploratory analysis yielded the following pre-specified covariates: reperfusion modality, age, anterior wall myocardial infarction, treatment with beta blockers, angiotensin receptor antagonists, or statins, and procedure timeliness (door-to-balloon time within 90 minutes, or door-to-needle time within 30 minutes for thrombolysis). Last, the Cox proportional hazard model was applied to evaluate treatment modalities while adjusting for the above covariates. The resulting hazard ratios along with 95% confidence intervals (95%CI) were presented as a forest plot. The significance of the three groups in the cox model was derived with the deviance of the log likelihood of adding treatment to the model (df = 2). SAS version 9.4 (Cary, NC, USA) and CRAN-R were used for analysis. A two-sided P value < 0.05 was considered statistically significant.

RESULTS

PRE-SPECIFIED REPERFUSION GROUPS

Of the 11,531 patients presenting with an acute coronary syndrome included in the six ACSIS registries, 5474 patients were diagnosed as STEMI, 5635 as non-STEMI, and 422 as unstable angina. Of the STEMI patients, 1464 met the study inclusion criteria. Of these, 899 were treated by PPCI, 383 by in-hospital TFA, and 182 by in-hospital thrombolysis only.

During the study period the mode of reperfusion treatment has changed with PPCI rates increasing from 54.7% in 2000 to 96.7% of patients in 2010. In addition, more thrombolysis-treated patients underwent coronary angiography during the index hospitalization. The baseline characteristics of the study population by reperfusion modality are presented in Table 1. Patients treated by PPCI were slightly older and tended to have more cardiovascular risk factors, with more anterior wall myocardial infarctions compared with thrombolysis-treated patients. Thrombolysis was administered to a higher proportion of STEMI patients admitted outside regular working hours (65.3% vs. 50.9%, $P < 0.001$) or during weekends (31.4% vs. 23%, $P = 0.005$), than in those admitted during working hours, who were treated more by PPCI.

TIME DELAYS

There was no difference among the three groups in the time interval that elapsed from symptom onset to hospital arrival. In both thrombolysis-treated groups, whether followed by angiography or not, the door-to-needle time was significantly shorter than the time from door-to-balloon inflation in the PPCI treated patients (median 45 and 52.5 vs. 63 minutes,

$P < 0.001$). Similarly, time from symptom-to-needle in the thrombolysis-treated patients with or without coronary angiography was shorter compared with time from symptom-to-balloon inflation (median 120 and 135 vs. 141 minutes, $P < 0.001$). Door-to-needle time of 30 minutes or less [2,3] was achieved in 26.7% of patients treated by TFA and in only 15.1% of thrombolysis only treated patients. In contrast, the recommended door-to-balloon time interval of less than 90 minutes was attained in 73.2% of patients treated by PPCI ($P < 0.01$).

IN-HOSPITAL MEDICAL THERAPY

The medical treatment administered during hospitalization and that was prescribed at discharge were not identical among study groups. Patients who underwent PPCI were treated more frequently with glycoprotein IIb/IIIa receptor antagonists (57%) during admission and more with clopidogrel (94%) and angiotensin receptor antagonists (57%) at discharge than thrombolysis-treated patients ($P < 0.001$). Virtually all patients received aspirin (99%). However, low molecular weight heparin and nitrates were administered more to the thrombolysis-treated patients ($P < 0.001$).

IN-HOSPITAL AND LONG-TERM OUTCOME

The median duration of hospitalization was longer in the thrombolysis treated patients (5 days for PPCI, 7 for TFA, and 6 for thrombolysis only, $P < 0.001$). More patients treated by TFA, compared to those treated by PPCI, were referred for bypass surgery (4.6% vs. 1.6%, $P < 0.001$), probably as a result of the non-urgent circumstances prevailing at the time of angiography. In-hospital echocardiography demonstrated a moderately or severely reduced left ventricle ejection fraction (LVEF) in 24.5% of PPCI patients compared with 28.6% of TFA patients and 31.9% of patients treated by thrombolysis only ($P = 0.1$). However, an echocardiogram was performed in 90% of patients in the PPCI and TFA groups during hospitalization, but fewer patients in the thrombolysis only group underwent such an analysis (91% for PPCI, 89% for TFA and 75% for thrombolysis only, $P < 0.001$ for all, $P = 0.14$ for PPCI vs. TFA).

The incidence of in-hospital complications and short- and long-term outcome are presented in Table 2. Compared with the PPCI patients a significant increase in post-infarction angina occurred among patients treated by TFA (11% in the TFA group vs. 2.7% in PPCI-treated patients and 3.3% for thrombosis only, $P < 0.01$). Free wall rupture occurred rarely but more frequently in patients treated by TFA ($P < 0.001$, Table 2). There was no significant difference in the incidence of in-hospital reinfarction, cerebrovascular accident, pulmonary edema, cardiogenic shock, stent thrombosis, renal failure and bleeding among the three groups, or specifically, between PPCI and TFA. The rate of the combined endpoint of death, reinfarction and angina at 30 days was significantly higher in the thrombolysis-treated patients, in both thrombolysis study groups compared with the PPCI (8.6% in the PPCI treated patients vs. 16.7% in the TFA and 19.8% in the thrombolysis only treated patients, $P < 0.001$). This difference was driven by an increased incidence of post-infarction angina, which probably was the trigger to perform coronary angiography in many cases.

The mortality in the TFA-treated patients at 7 and 30 days was the same as in the PPCI-treated patients. Similarly, there was no significant difference in mortality of groups at 1 year, although a clear tendency toward increased mortality at 30 days was observed in the thrombolysis only group. Multivariate analysis showed that the 30 day mortality of patients treated by PPCI was no different from that of patients treated by thrombolysis after adjusting for covariates. At 1 year, mortality in the PPCI and TFA patients was virtually the same with a non-significant increase in the thrombolysis only group [Table 2]. As for long-term prognosis, we present the Kaplan–Meier survival curves [Figure 1] and the predictors of 5 and 10 year mortality [Figure 2]. The hazard ratios for adjusted 5 and 10 year mortality by therapeutic modality, with PPCI as reference, are shown. The adjusted mortality in

Table 1. Basic clinical and demographic characteristics

Characteristics	PPCI (n=899) n (%)	TFA (n=383) n (%)	Thrombolysis only (n=182) n (%)	*P* value, overall	*P* value, PPCI vs. TFA
Age (years)	58.8 ± 12	57.1 ± 10.5	61.5 ± 13.5	‹ 0.001	0.01
Female, N (%)	139 (15.5)	49 (12.8)	36 (19.8)	0.009	0.21
Hypertension	387 (43.2)	124 (32.5)	66 (36.7)	0.01	‹ 0.001
Diabetes	194 (21.7)	77 (20.2)	35 (19.3)	0.71	0.56
Dyslipidemia	511 (57.3)	199 (52.1)	80 (44.2)	‹0.001	0.08
Smoking	454 (50.8)	210 (55.4)	81 (45)	0.64	0.13
Family history	301 (34.7)	99 (26.2)	38 (21.2)	‹ 0.001	‹ 0.001
Myocardial infarction	166 (18.5)	64 (16.8)	28 (15.5)	0.54	0.46
Angina pectoris	187 (20.8)	74 (19.4)	39 (21.7)	0.78	0.56
S/P PCI	171 (19)	46 (12.1)	23 (12.7)	‹ 0.001	‹ 0.001
S/P CABG	13 (1.4)	9 (2.4)	9 (5)	0.02	0.25
HF	14 (1.6)	5 (1.3)	5 (2.8)	0.42	0.73
S/P CVA	32 (3.6)	10 (2.6)	6 (3.3)	0.69	0.39
PVD	38 (4.2)	15 (3.9)	7 (3.9)	0.95	0.8
Renal failure	25 (2.8)	10 (2.6)	4 (2.2)	0.9	0.87
Anterior MI	453 (50.4)	159 (41.5)	67 (36.8)	‹ 0.001	‹ 0.001
Time from symptom onset to first hospital ward (median, minutes)	110	105	120	0.08	0.42
Arrival during off-work hours	639 (73.9)	349 (98.6)	152 (83.5)	‹ 0.001	‹ 0.001

PPCI = Primary PCI, TFA = thrombolysis followed by angiography, PCI = percutaneous coronary intervention, CABG =Coronary artery bypass grafting, HF = Heart failure, CVA = cerebrovascular accident, PVD = Peripheral vascular disease, MI = myocardial infarction, off-working hours = 16:00–08:00 and weekends

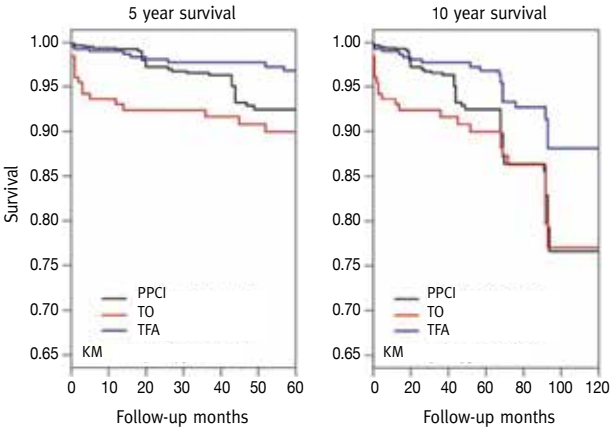
S/P = status post

Table 2. In-hospital complications and short- and long-term prognosis following reperfusion

In hospital complications	PPCI (n=899) N (%)	TFA (n=383) N (%)	TO (n=182) N (%)	*p* value, overall	*p* value, PPCI vs. TFA
Re-infarction	13 (1.5)	11 (2.9)	4 (2.2)	0.22	0.08
Post-infarction angina	24 (2.7)	42 (11)	6 (3.3)	‹ 0.001	‹ 0.001
Pulmonary edema	26 (2.9)	12 (3.1)	5 (2.7)	0.96	0.80
Cardiogenic shock	17 (1.9)	5 (1.3)	3 (1.6)	0.75	0.46
Bleeding	12 (1.3)	4 (1)	2 (1.1)	0.89	0.66
Free wall rupture	1 (0.1)	2 (0.5)	5 (2.7)	<0.001	0.16
Tamponade	1 (0.1)	1 (0.3)	1 (0.5)	0.47	0.53
VSD	1 (0.1)	1 (0.3)	1 (0.5)	0.47	0.53
Subacute thrombosis	13 (2.2)	1 (1.2)	0 (0)	0.71	0.56
High-degree atrial ventricular block	27 (3)	12 (3.1)	10 (5.5)	0.23	0.89
CVA/TIA	7 (0.8)	1 (0.3)	3 (1.6)	0.20	0.28
Acute renal failure	24 (2.7)	7 (1.8)	7 (3.8)	0.36	0.37
Short- and long-term prognosis					
7 day mortality	10 (1.1)	3 (0.8)	8 (4.4)	‹ 0.001	0.59
30 day mortality	17 (1.9)	7 (1.8))	9 (4.9)	0.03	0.93
One year mortality	27 (3)	13 (3.4)	11(6.1)	0.12	0.73
30 day MACE	77 (8.6)	64 (16.7)	36 (19.8)	‹ 0.001	‹ 0.001
Follow-up (months) (median, 1st–3rd quartile)	38.6 ± 30 (20, 19–68)	64.4 ± 39 (68, 29–93)	64.9 ± 43 (69, 20–104)	‹ 0.001	

PCI = percutaneous coronary intervention, PPCI = primary PCI, TFA = thrombolysis followed by angiography, TO = thrombolysis only, MACE = death, post-infarction angina, myocardial infarction, VSD = ventricular septal defect, CVA/TIA = cerebrovascular accident/ transient ischemic attack

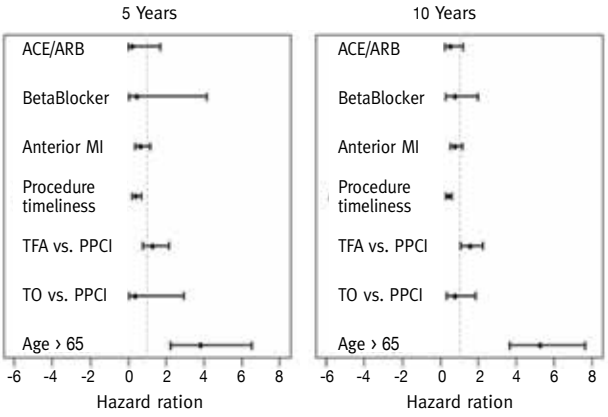
Figure 1. The 5 year and 10 year survival curves according to reperfusion modality



PCI = percutaneous coronary intervention, PPCI = primary PCI, TFA = thrombolysis followed by angiography, TO = thrombolysis only, d/f = degrees of freedom, d = number of deaths

KM = significance of difference of Kaplan–Meier curves

Figure 2. Forest plot for the hazard ratio and the 95% confidence interval of the predictors for 5 year and 10 year mortality by Cox regression analysis



ACE/ARB = angiotensin-converting enzyme/angiotensin-receptor blocker, MI = myocardial infarction, PCI = percutaneous coronary intervention, PPCI = Primary PCI, TFA = thrombolysis followed by angiography, TO = thrombolysis only

the TFA patient group was significantly lower at 5 years (P = 0.05) and 10 years (P = 0.04) compared with the mortality in the PPCI-treated patients.

DISCUSSION

Over the last 15 years, treatment of STEMI shifted from thrombolysis administered to most STEMI patients to PPCI as an almost exclusive therapy. Studies that demonstrated the superiority of PPCI over thrombolysis also included high-risk, late-arriving patients. Furthermore, many thrombolysis-treated STEMI patients in these trials did not undergo coronary angiography at all during hospitalization [1].

The current study shows that in early arriving hemodynamically stable STEMI patients admitted to PCI-capable hospitals, PPCI was superior to TFA and to thrombolysis only with regard to the composite outcome of death, post-infarction angina and myocardial infarction, but not with regard to long-term mortality. The fact that TFA yielded, in this particular subgroup of stable early arriving STEMI patients, a 1 year survival comparable to that achieved by PPCI seems, despite some limitations, reliable and is supported by a substantial body of published

evidence. Moreover, in this select group TFA yielded a better long-term survival than that achieved by PPCI [Figure 1].

Previous studies demonstrated that the time from symptom onset to first medical contact or to reperfusion [7-9,13], patient risk profile [13,14], and angiography performed after successful thrombolysis on a mandatory basis or only as rescue PCI when thrombolysis fails [4,5] greatly influence patient outcome when comparing thrombolysis to PPCI. As expected, the present study confirmed that timeliness of therapy and age impacted significantly on outcome [Figure 2].

The data on the influence of the reperfusion modality on outcome in early-arriving STEMI patients are somewhat conflicting. Zijlstra et al. [15] demonstrated the advantage of PPCI over thrombolysis in patients presenting within 2 to 3 hours, whereas the PRAGUE-2 trial showed better outcome with PPCI compared to thrombolysis only in patients treated after 3 hours from symptom onset [9]. The CAPTIM trial demonstrated that PPCI was no better than pre-hospital thrombolysis in STEMI patients presenting within 6 hours from symptom onset. The majority of thrombolysis-treated patients in this trial underwent angiography during hospitalization with rescue PCI performed when indicated. In a 5 year follow-up of the CAPTIM trial, the observed survival in patients presenting within 2 hours from symptoms onset and treated by pre-hospital thrombolysis was significantly higher compared with that observed in patients treated by PPCI [8]. The randomized Strategic Reperfusion Early after Myocardial Infarction (STREAM) study found that STEMI patients arriving within 3 hours from symptom onset and treated by PPCI or pre-hospital thrombolysis when PPCI could not be performed within 60 minutes of arrival, achieved similar results with respect to the primary composite endpoint of death, shock, congestive heart failure, or reinfarction within 30 days [10]. The lack of difference in the 30 day incidence of reinfarction was attributed to the requirement to perform angiography within 24 hours in all thrombolysis-treated patients and to the obligatory use of P2Y12 blockers. However, a higher incidence of intracranial bleeding was observed in patients treated by thrombolysis in the STREAM study, a finding consistent with therapy of elderly patients (> 75 years) with tenecteplase [10]. This result is in contrast to current study, which included a younger patient population and used mostly streptokinase, known to cause less intracranial bleeding than fibrin-specific agents [1].

A study that evaluated the effect of patient risk on outcome in STEMI patients, treated by either PPCI or thrombolysis, found no difference in mortality in low risk patients (TIMI risk score 0–4), whereas a significant reduction in mortality was observed in high-risk patients (TIMI risk score > 4) treated by PPCI [14]. Registries, such as the FAST-MI, comparing the clinical efficacy of thrombolysis with PPCI, have shown similar outcomes, provided angiography was performed during hospitalization in a large proportion of thrombolysis-treated patients [12]. A Canadian registry found similar in-hospital death rates in STEMI patients treated by PPCI or by thrombolysis followed by angiography and lower survival if treated with thrombolysis alone [11].

A door-to-balloon time of less than 90 minutes was achieved in the majority of patients in this study. However, thrombolytic therapy, which is so readily available and so easy to administer, achieved current guidelines-recommended door-to-needle time of less than 30 minutes in only 26.7% of patients treated by TFA and in a dismal rate of 15.1% in those treated by thrombolysis only. And yet, the results show that in-hospital thrombolysis-treated STEMI patients followed by angiography achieved short- and long-term mortality rates comparable to those of PPCI-treated patients. Adherence to guidelines-required door-to-needle time of 30 minutes could have plausibly reduced mortality of TFA-treated patients even further. The 1 year survival of patients treated by thrombolysis only, however, tended to be lower compared to the other treatment modalities (P = NS, Table 2). The 30 day composite endpoint of death, post-infarction angina and myocardial infarction, driven mainly by the increased rate of post-infarction angina, was higher in thrombolysis-treated patients. In our opinion, early and prompt coronary intervention following successful thrombolysis could have obviated this occurrence rendering both therapeutic modalities compatible even with respect to MACE.

Another consideration that can improve the results of thrombolysis is a requirement to perform rescue intervention in any case of doubtful recanalization of the culprit artery. Such a policy might also reduce the incidence of post-infarction angina in TFA treated patients. A meta-analysis of seven randomized trials found that routine early PCI after thrombolysis was superior to delayed or ischemia-guided PCI, resulting in reduction of reinfarction and recurrent ischemia [4]. The salutary effect of rescue PCI in STEMI patients in whom thrombolysis failed was shown in another meta-analysis [5].

In general, thrombolysis is efficacious and achieves high patency rate when administered early, whereas the benefit of the high rate of recanalization by PPCI (> 95%) may be slightly offset by frequent microvascular embolization and dysfunction following mechanical revascularization [16]. Thrombolysis should be administered within 30 minutes of admission followed by definitive intervention performed as earliest as feasible. These could increase coronary patency improving prognosis, and decreasing considerably the incidence of post-infarction angina whose occurrence increased the rate of MACE among thrombolysis-treated patients in the present registry. Thus, current results show that in-hospital TFA may yield a 1 year survival comparable to that of PPCI-treated patients, and better long-term survival [Figure 1] in this select subgroup of patients. These outcomes could probably be improved even further if thrombolysis would have been administered expeditiously in accordance with guidelines.

LIMITATIONS

A limitation of the study is its design as a registry with no randomization, although it has the advantage of a real-life all-comers study. Most patients treated with thrombolysis were hospitalized in the first half of the decade when standard treatment was different compared to the second half of the decade with regard to the wider use of statins, beta blockers, angiotensin-converting enzyme (ACE) inhibitors and P2Y12 receptor antagonists. There is a lack of data concerning the reason for performing angiography in the thrombolysis-treated patients, whether done due to thrombolysis failure, post-infarction angina or ischemia or merely as a routine procedure. The data also do not include details of the clinical reperfusion success rate of the thrombolysis treatment. Although selection bias cannot be ruled out in this registry, the 5 and 10 year survival of the TFA group was significantly higher in the TFA group even after adjustment and is in agreement with the long-term CAPTIM results.

CONCLUSIONS

PPCI treatment in early arriving low-risk STEMI patients resulted in less MACE, driven mainly by less post-infarct angina, compared to thrombolysis, but with similar 7 day, 30 day or 1 year survival to treatment with TFA. Five and 10 year mortality rates were even lower in TFA-treated patients. Although feasibly underpowered, due to the small number of thrombolysis-treated patients, these findings are in accord with previous studies and demonstrate that in this specific population, thrombolysis may be used as an alternative to PPCI, especially in the absence of immediate interventional capability.

Correspondence
Dr. S.R. Meisel
Heart Institute, Hillel Yaffe Medical Center, Hadera 38100, Israel
Phone: (972-4) 630-4419
Fax: (972-4) 630-4422
email: meisel@hy.health.gov.il

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"If we value independence, if we are disturbed by the growing conformity of knowledge, then we may wish to set up conditions of learning which make for uniqueness"

Carl Rogers (1902–1987), American psychologist considered to be one of the founding fathers of psychotherapy research

"As you grow older, you will discover that you have two hands, one for helping yourself, the other for helping others"

Audrey Hepburn (1929–1993), British actress, model, dancer and humanitarian. Recognized as a film and fashion icon