Long-Term Outcomes in ST Elevation Myocardial Infarction Patients Undergoing Coronary Artery Bypass Graft Versus Primary Percutaneous Coronary Intervention

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ABSTRACT **Background:** Coronary artery bypass grafting (CABG) for primary reperfusion in patients with ST elevation myocardial infarction (STEMI) has largely been superseded byf primary percutaneous coronary intervention (PCI) and is estimated to be performed in ≤ 5% of STEMI cases.

Objectives: To compare early CABG (within 30 days following admission) and primary PCI outcomes following STEMI.

Methods: We analyzed a retrospective cohort of patients hospitalized with acute STEMI for early reperfusion therapy between January 2008 and June 2016. Short- and long-term outcomes were assessed for patients with STEMI undergoing primary PCI vs. early CABG as reperfusion therapy.

Results: The study comprised 1660 STEMI patients, 38 of whom (2.3%) underwent CABG within 30 days of presentation. Unadjusted 30-day mortality was more than twice as high in the CABG group (7.5%) than in the PCI group (3.3%); however, it did not reach statistical significance. Similar results were demonstrated for mortality rates beyond 30 days (22% vs. 14%, $P = 0.463$). All patients undergoing CABG beyond 72 hours following admission survived past 2 years. Multivariate analysis found no differences between the two groups in long-term mortality risk. propensity score matched long-term mortality comparison (30 days–2 years) yielded a 22% mortality rate in the CABG groups compared with 14% in the PCI group ($P < 0.293$).

Conclusion: Early CABG was performed in only a minority of STEMI patients. This high-risk patient population demonstrated worse outcomes compared to patients undergoing PCI. Performing surgery beyond 72 hours following admission may be associated with lower risk.

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KEY WORDS: coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), ST elevation myocardial infarction (STEMI)

Among patients presenting with ST elevation myocardial infarction (STEMI), guideline-based management includes early reperfusion using fibrinolytic therapy or primary percutaneous coronary intervention (PCI) [1,2]. Multiple randomized control trials have found a survival benefit and lower rates of recurrent ischemic events favoring PCI over fibrinolysis [3,4]. Current guidelines recommend the use of primary PCI for any patient with an acute STEMI who can undergo the procedure in a timely manner by an experienced catheterization team [5]. The practice of coronary artery bypass grafting (CABG) as primary reperfusion in STEMI patients has largely been superseded and as a result and it has been estimated that urgent CABG is presently performed in less than 5% of STEMI cases [6]. STEMI patients referred for early CABG usually include patients in whom PCI failed to provide reperfusion, patients with mechanical complications, and those with refractory ischemia or cardiogenic shock with severe multi-vessel disease [5]. While large data exists on clinical outcomes of CABG in patients with acute coronary syndromes [7-9], limited research has studied the clinical outcomes of STEMI patients undergoing CABG [10,11]. Our aim was to examine the incidence, characteristics, and clinical outcomes of early CABG surgery as compared to PCI for early reperfusion therapy.

PATIENTS AND METHODS

STUDY POPULATION

A retrospective, single center observational study was performed at the Tel Aviv Sourasky Medical Center, a tertiary referral hospital with a 24/7 primary PCI service. We analyzed the medical records of 1779 patients admitted between January 2008 and June 2016 to the cardiac intensive care Unit (CICU) with the diagnosis of acute STEMI. We excluded 37 patients treated either conservatively or by thrombolysis only and 82 patients whose final diagnosis on discharge was other than STEMI (e.g., myocarditis or Takotsubo cardiomyopathy). The final study population thus included 1660 patients whose baseline demographics, cardiovascular history, clinical risk factors, treatment characteristics, and laboratory results were all retrieved from the hospital electronic medical records without any missing data. The diagnosis of STEMI was established according to published guidelines including a typical history of chest pain, diagnostic electrocardiographic changes, and serial elevation of cardiac biomarkers [5]. Primary PCI was performed in patients presenting with symptoms ≤ 12 hours in duration as well as in patients with symptoms lasting 12–24 hours in duration provided that symptoms persisted at the time of admission. Time to coronary reperfusion was defined as the period between symptom onset (usually chest pain or discomfort) as recorded upon admission and until the restoration of perfusion, as reported in the catheterization laboratory report. Coronary artery disease was defined according to current guidelines [12] by a coronary lumen stenosis of over 70% considered as significant. Critical state was defined as cardiogenic shock requiring treatment with positive inotropes, intra-aortic balloon counter pulsation (IABP) or mechanical ventilation. Left ventricular ejection fraction was assessed in all patients by bedside echocardiography within the first 48 hours of admission. Renal dysfunction has been described in detail previously[13]. Assessment of survival following hospital discharge was collected from computerized records of the population registry bureau. Patient records were surveyed for outcomes of early CABG procedures, defined as performed within 30 days following hospitalization for STEMI. The study protocol was approved by the local institutional ethics committee (IRB # TLV 16-224, p) and individual informed consent was obtained.

INDICATIONS FOR CABG AND CABG OUTCOMES

The decision to perform CABG was made by a multidisciplinary cardiac team consisting of a cardiothoracic surgeon, an interventional cardiologist, and a clinical cardiologist, according to guidelines available during the time of the procedure [14-16]. CABG operations were considered for patients with persistent or recurrent ischemia refractory to treatment with PCI and medical therapy, patients with cardiogenic shock when performed as a concomitant procedure to a post-infarction ventricular septal rupture or mitral valve insufficiency, or as primary reperfusion therapy within 24 hours if the coronary anatomy was unsuitable for PCI. In addition, CABG was performed in the absence of ischemia when an anatomical indication was present, in accordance with current guidelines [14]. Anatomical indications were defined as significant left main coronary artery stenosis, three-vessel disease and two-vessel disease with significant involvement of the proximal left anterior descending coronary artery, and either depressed left ventricular function or noninvasive evidence of ischemia. The internal thoracic artery, radial artery, and saphenous vein grafts were used as graft conduits. IABP support was liberally applied according to coronary artery morphology.

STATISTICAL ANALYSIS

Categorical variables were expressed as percentages and continuous variables were presented as mean ± SD. Continuous variables were tested for normal distribution. Categorical variables were compared using Chi-square test or Fisher's exact test, and continuous variables were compared between groups using the independent *t*-test analysis or Mann-Whitney test. Cumulative survival was first assessed using a log-rank test. Binary logistic regression was used to assess the link between timing and mortality. A multivariate analysis using the Cox regression model was performed according to age, smoking history, hypertension, coronary artery disease, diabetes mellitus, creatinine on admission, and C-reactive protein (CRP) levels. We performed a propensity matched analysis according to age, gender, diabetes, hyperlipidemia, family history, smoking history, past MI, extent of coronary artery disease and creatinine levels, producing two groups of 38 patients each. A two-tailed $P < 0.05$ was considered statistically significant. Analyses were performed with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

BASELINE

The patient population included 1660 STEMI patients. CABG was performed in 38 (2.3%) within 30 days of presentation. Among these patients, the procedure was performed in four patients (10%) within 24 hours of presentation due to failed PCI. Among the other 34 patients, thrombolysis in myocardial infarction grade 3 flow was demonstrated in the culprit artery at the onset of angiography, or PCI to the culprit artery was performed and followed by CABG for residual disease. Of these, CABG was performed in 14/34 patients (41%) between days 1–3 following presentation and in 20/34 patients (59%) from days 4 to 30 following presentation. CABG patient characteristics are outlined in Table 1. All patients underwent CABG according to guidelines, 82% due to vascular indications, mainly multi-vessel disease and left main coronary artery stenosis, followed by failed PCI due to mechanical complications (5%) or mixed indications (5%). In our cohort, 33/38 patients (87%) underwent a coronary bypass of 2 to 4 coronary arteries. For 22/38 patients (58%), the left internal mammary artery (LIMA) alone was used as a graft. Baseline and clinical characteristics of patients undergoing early CABG and patients undergoing primary PCI are shown in Table 2. Patients undergoing CABG were more likely to be hypertensive and diabetic and also have more chronic kidney disease and higher baseline C-reactive protein at baseline. In addition, patients undergoing early CABG were more likely to have lower ejection fraction, present with heart failure and were also more likely to be hemodynamically unstable, requiring mechanical ventilation or treatment with intravenous inotropes and/or an IABP prior to surgery.

IN HOSPITAL AND LONG-TERM OUTCOMES

Table 3 displays in-hospital adverse events for both study groups. Unadjusted 30-day mortality was more than twice as high in the CABG group (3/38, 7.5%) than in the PCI group, (55/1622, 3.3%), but given the small number of patients in the CABG group, the difference is was not significant. Clinical follow-up for long-term mortality was analyzed for a duration of up to 24 months. Mortality rates of patients who have survived beyond 30 days were not significantly different between CABG and PCI patients (8/35 [23%] vs. 219/1567 [14%], hazard ratio = 0.767, 95%

confidence interval = 0.378–1.557, $P = 0.463$]. Examination of the association between the timing of surgery and mortality was performed using a binary logistic regression model in which the continuous variable is time and the binary variable is all cause mortality. Once more, the above analysis yielded a statistically insignificant result ($P = 0.729$). Of the 11 CABG patients who died, 5 (45%) were operated on within 24 hours of admission. The remaining six patients (55%) were operated on within 24–72 hours. There were no mortality cases for patients undergoing the operation beyond 72 hours following admission. A multivariate analysis comparison using a Cox regression model demonstrated no difference between the PCI and CABG treatment groups in long-term mortality (excluding patients who died within the first 30 days) after adjustment for age, smoking history, hypertension, coronary artery disease, diabetes mellitus, creatinine on admission and CRP. We also compared the CABG and the PCI treatment groups by propensity score matching according to age, gender, diabetes, hyperlipidemia, family history, smoking history, past MI, extent of coronary artery disease, and creatinine levels; Thus, two groups of 38 patients each were compared for 30-day mortality with 3/38 mortality cases in the CABG group compared with 2/38 mortality cases in the PCI group (8% vs. 5%, $P = 0.999$). Comparing long-term mortality beyond 30 days and up to 2 years, there were 8/35 mortality cases in the CABG group compared with 5/36 in the PCI group (23% vs. 14%, $P = 0.293$).

Table 1. CABG patient characteristics (n=38)

n (%)	Indication for CABG
31 (82%)	Vascular
2 (5%)	Mechanical complication
3 (8%)	Mixed
2 (5%)	Other
	Number of grafts
4 (11%)	1
33 (87%)	2-4
	Graft type
22 (58%)	LIMA
14 (37%)	LIMA + RIMA

CABG = coronary artery bypass graft, LIMA = left internal mammary artery, RIMA = right internal mammary artery

Table 2. Baseline and clinical characteristics of STEMI patients stratified by procedure

Variable	CABG (n=38)	Primary PCI (n=1622)	*P* value*
Age (years), mean ± SD	65.4 ± 12.6	61.4 ± 12.9	0.83
Male	36 (95%)	1342 (83%)	0.15
Diabetes mellitus	18 (47%)	398 (25%)	**0.002**
Hypertension	24 (63%)	716 (44%)	**0.03**
Hyperlipidemia	22 (58%)	791 (49%)	0.36
Smoker	15 (39%)	847(52%)	0.08
Chronic kidney disease	13 (34%)	252 (16%)	**0.01**
Family history of CA	15 (39%)	360 (22%)	0.3
Prior myocardial infarction	8 (21%)	243 (15%)	0.35
Number of narrowed coronary arteries	1: 3 (8%)	1: 670 (41%)	**<0.001**
	2: 5 (13%)	2: 492 (30%)	
	3: 30 (79%)	3: 481 (30%)	
Ejection fraction, (%), mean ± SD	40 ± 9	48 ± 8	**<0.001**
Heart failure	16 (42%)	162 (10%)	**<0.01**
IABP and/or inotropes	15 (39%)	60 (4%)	**<0.01**
Mechanical ventilation	9 (24%)	80 (5%)	**<0.01**
Admission sCr (mg/dl)	1.23 ± 0.37	1.11 ± 0.32	0.09
Admission hemoglobin (g/dl), mean ± SD	13.8 ± 1.8	14.3 ± 1.6	0.06
Admission CRP (mg/dl), mean ± SD	25.5 ± 40	13 ± 29.5	**0.01**
Peak CPK (Units/L), mean ± SD	1154.3 ± 1197.8	1323.2 ± 1519.8	0.58
Troponin max (ng/ml), mean ± SD	12600 ± 52800	21600 ± 76700	0.27

*Bold indicates significance
CAD = coronary artery disease, CPK = creatine phosphokinase, CRP = C-reactive protein, IABP = intra-aortic balloon counter pulsation, sCr = serum creatinine levels

Table 3. In-hospital complications for STEMI patients

Variable	CABG (n=38)	Primary PCI (n=1622)	*P* value*
Brady-arrhythmia	3 (8%)	85 (5%)	0.5
Ventricular tachycardia or ventricular fibrillation	4 (11%)	124 (8%)	0.55
Atrial fibrillation	2 (5%)	72 (4%)	0.84
In stent thrombosis after primary PCI	4 (11%)	80 (5%)	0.13
Acute kidney injury	7 (18%)	130 (8%)	**< 0.001**
Major bleeding	9 (24%)	77 (5%)	**< 0.01**
30-day mortality	3 (8%)	55 (3%)	0.15

*Bold indicates significance
CABG = coronary artery bypass graft, PCI = percutaneous coronary intervention

DISCUSSION

In this large cohort of STEMI patients, early CABG (performed within 30 days after presentation) was performed in only a minority of patients. This finding is in accordance with previous studies and experience [17-19]. Patients undergoing CABG represented a high-risk group with a more significant coronary artery disease burden and were more prone to hemodynamic instability. Most patients included in our study had the procedure performed within 4 to 30 days after their initial hospital admission for STEMI.

Early CABG surgery once played a more dominant role in the management of selected patients presenting with STEMI [18]. Accumulating experience and progress in catheterization techniques has steadily decreased the need for surgical revascularization in patients presenting with STEMI in the past decades [18,19] and urgent CABG is now performed in less than 5% of STEMI cases [6]. This paradigm shift is mainly attributed to developments in interventional cardiology such as the use of new generation drug eluting stents and dual antiplatelet therapy [20,21]. Current guidelines suggest surgical revascularization for STEMI mainly for failed PCI, ongoing ischemia refractory to non-surgical treatment, cardiogenic shock with severe multi-vessel disease, and mechanical complications [21]. The main finding of the current study is that, despite the high-risk and unfavorable in-hospital course, long-term outcomes of patients treated with early CABG were similar to patients treated with PCI.

Outcomes have been found to be directly related to the timing of the procedure in previous studies [6-8,21-24]. Thielmann et al. [22] demonstrated optimal surgical results when CABG is conducted at timely intervals with a 10.8% mortality rate for patients in whom CABG was performed < 6 hours from onset of symptoms compared with 2.4% when performed 8 to 14 days following onset of symptoms. In another study, mortality rates for patients operated within the first 24–72 hours following STEMI were significantly increased [8]. A major finding of our study is that all patients who underwent CABG over 72 hours after onset of symptoms survived beyond 2 years. This finding might be explained by patients being better stabilized prior to surgery, improving their chances of surviving. However, this situation could also be explained by urgency, as higher severity patients might have undergone surgery earlier in the course of their disease compared to lower-risk patients, explaining the differences in mortality, although these differences did not reached statistical significance in our study.

In our study, CABG was performed within 4–30 days of presentation in more than half of the patients. In addition to surgery timing, several other factors emerged as predictors for adverse outcomes in STEMI patients undergoing CABG: age, female gender, preoperative cardiogenic shock or heart failure, CABG after failed PCI or fibrinolysis, and the degree of preoperative myocardial injury as quantified by cardiac troponin [19-21,25]. Consistent with Freundlich et al. [23], in our study the CABG cohort included very high-risk patients who were more likely to present with cardiogenic shock, ventricular arrhythmia, acute kidney injury, and major bleeding, especially in first 3 days from onset of STEMI [6]. In contrast to Milojevic and colleagues [24], we found that patients undergoing CABG had similar long-term mortality rates, a result that persisted after adjusting for confounders and for the higher in-hospital complication rates, although the absolute number of mortalities was higher, and the insignificant result may stem from the small cohort of CABG patients in our study. We also found no differences in short-term and long-term mortality rates, after exclusion of patients who did not survive beyond 30 days. We assume that improved technology and equipment, in combination with proper stabilization and optimized medical treatment prior to the procedure, contributed to the improved outcomes in these patients. In addition, improvement in medical infrastructure and better treatment of short-term post-CABG complications also contributed to improved long-term outcomes.

Our study has several notable limitations. Foremost, the small number of patients in the CABG group and specifically the low numbers of early CABG operations performed may have influenced results and limit the power of the statistical analyses and the conclusions that can be drawn from the study, hence the results should be interpreted with caution and require corroboration. The small number of patients may have also exposed the study to a selection bias.

In addition, this single center, retrospective, non-randomized, observational study may have been subject to bias, although consecutive patients were included and we attempted to adjust for confounding factors. In addition, the following valuable data was missing and might have influenced assumptions and conclusions: data regarding the syntax score, which plays a major role in the decision regarding the preferred revascularization method was not available, as well as data on causes of mortality, recurrent myocardial infarction and revascularization.

CONCLUSIONS

Early CABG was performed in only a minority of STEMI patients. This high-risk patient population demonstrated worse outcomes compared to patients undergoing PCI. It appears that performing surgery beyond 72 hours following admission may be associated with lower risk. Further studies with larger cohorts are needed to validate our conclusions.

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There is nothing like a dream to create the future.

Victor Hugo (1802–1885), French poet, playwright,
novelist, statesman, human rights activist