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Journal of the American College of Cardiology Vol. 58, No. 7, 2011
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.02.071

Prognostic Impact of Staged Versus "One-Time" Multivessel Percutaneous Intervention in Acute Myocardial Infarction

Analysis From the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) Trial

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Objectives The purpose of this study was to compare a one-time primary percutaneous coronary intervention (PCI) of the culprit and nonculprit lesions with PCI of only the culprit lesion and staged nonculprit PCI at a later date in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease.

Background In patients with STEMI and multivessel disease, it is unknown whether it is safe or even desirable to also treat the nonculprit vessel during the primary PCI procedure.

Methods In the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial, 668 of the 3,602 STEMI patients enrolled (18.5%) underwent PCI of culprit and nonculprit lesions for multivessel disease. Patients were categorized into a single PCI strategy (n = 275) versus staged PCI (n = 393). The endpoints analyzed included the 1-year rates of major adverse cardiovascular events and its components, death, reinfarction, target-vessel revascularization for ischemia, and stroke.

Results Single versus staged PCI was associated with higher 1-year mortality (9.2% vs. 2.3%; hazard ratio [HR]: 4.1, 95% confidence interval [CI]: 1.93 to 8.86, $p < 0.0001$), cardiac mortality (6.2% vs. 2.0%; HR: 3.14, 95% CI: 1.35 to 7.27, $p = 0.005$), definite/probable stent thrombosis (5.7% vs. 2.3%; HR: 2.49, 95% CI: 1.09 to 5.70, $p = 0.02$), and a trend toward greater major adverse cardiovascular events (18.1% vs. 13.4%; HR: 1.42, 95% CI: 0.96 to 2.1, $p = 0.08$). The mortality advantage favoring staged PCI was maintained in a subgroup of patients undergoing truly elective multivessel PCI. Also, the staged PCI strategy was independently associated with lower all-cause mortality at 30 days and at 1 year.

Conclusions A deferred angioplasty strategy of nonculprit lesions should remain the standard approach in patients with STEMI undergoing primary PCI, as multivessel PCI may be associated with a greater hazard for mortality and stent thrombosis. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966) (J Am Coll Cardiol 2011;58:704–11) © 2011 by the American College of Cardiology Foundation

Coronary reperfusion through the expeditious use of primary percutaneous coronary intervention (PCI) targeted primarily at the culprit lesion improves the outcome of patients with ST-segment elevation myocardial infarction

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(STEMI) (1). However, in STEMI patients, multivessel coronary disease is often encountered and poses a therapeutic dilemma, for example, whether to treat the nonculprit lesion/vessel at the same setting. In nonshock STEMI patients, the American College of Cardiology/American Heart Association and European Society of Cardiology guidelines support the use of primary PCI directed only at the infarct-related artery, with PCI of the nonculprit lesions guided by objective evidence of residual ischemia at later follow-up (2,3). Since large-scale, prospective randomized clinical trials are lacking to guide the appropriateness of complete revascularization during the course of STEMI, it is yet unknown whether it is safe or even desirable to also treat the nonculprit vessel during the acute infarction phase.

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The large-scale prospective HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial randomly assigned STEMI patients undergoing primary PCI to bivalirudin alone compared to heparin plus a glycoprotein IIb/IIIa inhibitor (GPI), and to the use of TAXUS Express paclitaxel-eluting stents versus Express bare metal stents (both Boston Scientific, Natick, Massachusetts) (4–6). We, therefore, analyzed the HORIZONS-AMI database to explore the impact of a single "1-time" intervention (PCI of culprit and nonculprit lesions together) versus PCI of the culprit lesion only with staged nonculprit PCI at a later date.

Methods

Study protocol. The HORIZONS-AMI study design has been previously described in detail (4–6). In summary, the HORIZONS-AMI study was a prospective, open-label, randomized, multicenter trial in which 3,602 patients with STEMI presenting within 12 h of symptom onset and undergoing a primary PCI management strategy were randomly allocated equally in the emergency department using a computerized interactive voice response system to bivalirudin alone versus unfractionated heparin plus a GPI (the control group). After angiography, eligible patients were randomly allocated again in a 3:1 ratio to either TAXUS Express paclitaxel-eluting stents or otherwise identical uncoated Express bare metal stents. The study was approved by the institutional review board or ethics committee at each participating center, and all patients signed informed consent.

Abbreviations and Acronyms

AMI = acute myocardial infarction
GPI = glycoprotein IIb/IIIa inhibitor
LVEF = left ventricular ejection fraction
MACE = major adverse cardiovascular event(s)
NACE = net adverse clinical event(s)
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Patient eligibility has also been described previously (4–6). In summary, consecutive patients ≥18 years of age with symptom onset within 12 h of duration and ST-segment elevation of ≥1 mm in ≥2 contiguous leads, new left bundle branch block, or true posterior MI were considered for enrollment. Principal exclusion criteria included contraindications to any of the study medications; prior administration of fibrinolytic therapy, bivalirudin, GPI, low molecular weight heparin, or fondaparinux for the present admission (prior unfractionated heparin was allowed); current use of warfarin; history of bleeding diathesis, conditions predisposing to hemorrhagic risk, or refusal to receive blood transfusions; stroke or transient ischemic attack within 6 months or any permanent neurologic deficit; recent or known platelet count <100,000 cells/mm^3 or hemoglobin <10 g/dl; planned elective surgical procedure that would necessitate interruption of thienopyridines during the first 6 months after enrollment; coronary stent implantation within 30 days; and noncardiac comorbid conditions with life expectancy <1 year or that might result in protocol noncompliance.

Clinical follow-up was pre-specified at 30 days, at 1 year, and yearly thereafter for 3 years total in all patients, with the exception of patients in whom all measured cardiac biomarkers were within normal limits and no coronary artery lesions were present with a diameter stenosis >50% by core laboratory determination; these patients required only 30-day follow-up.

Patients and study analysis. Of the 3,602 STEMI patients enrolled in the trial, 668 patients (18.5%) underwent PCI for multivessel coronary artery disease. Per operator discretion, PCI of the nonculprit lesions and vessels could be performed either during the acute infarct procedure (after successful treatment of the infarct-related artery), or in a separate staged procedure. A total of 275 patients (41%) underwent a 1-time multivessel procedure, whereas staging was performed in 393 (Fig. 1A). Patients undergoing multivessel PCI were further stratified by excluding from both groups all patients in whom the second lesion was in a vessel with Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 2, in whom emergent nonculprit PCI might have been required. This latter classification thus defined 2 "true elective" multivessel PCI groups, namely, 165 patients

has received consulting fees from or has served on advisory boards for Abbott Vascular, Boston Scientific, Volcano, and Cordis; and receives grant support from Medtronic, Boston Scientific, Abbott, Lightlab, and Labcoat. Dr. Dudek reports receiving lecture fees from Nycomed; and research grants from or served as consultant/advisory board member for Abbott, Adamed, Biotronik, Balton, Bayer, BBRaun, BioMatrix, Boston Scientific, Boehringer Ingelheim, Bristol-Myers Squibb, Cordis, Cook, Eli Lilly, EuroCor, GlaxoSmithKline, Invatec, Medtronic, The Medicines Company, MSD, Nycomed, Orbus-Reich, Pfizer, Possis, Promed, Sanofi-Aventis, Siemens, Solvay, Terumo, and Tyco. Drs. Fahy and Lansky report being employed by the Cardiovascular Research Foundation. Dr. Stone reports receiving consulting fees from Medtronic, GlaxoSmithKline, Eli Lilly, and Bristol-Myers Squibb, and grant support from Boston Scientific, The Medicines Company, and Abbott Vascular. All other authors have reported that there are no relationships to disclose.

Manuscript received September 19, 2010; revised manuscript received February 14, 2011, accepted February 22, 2011.

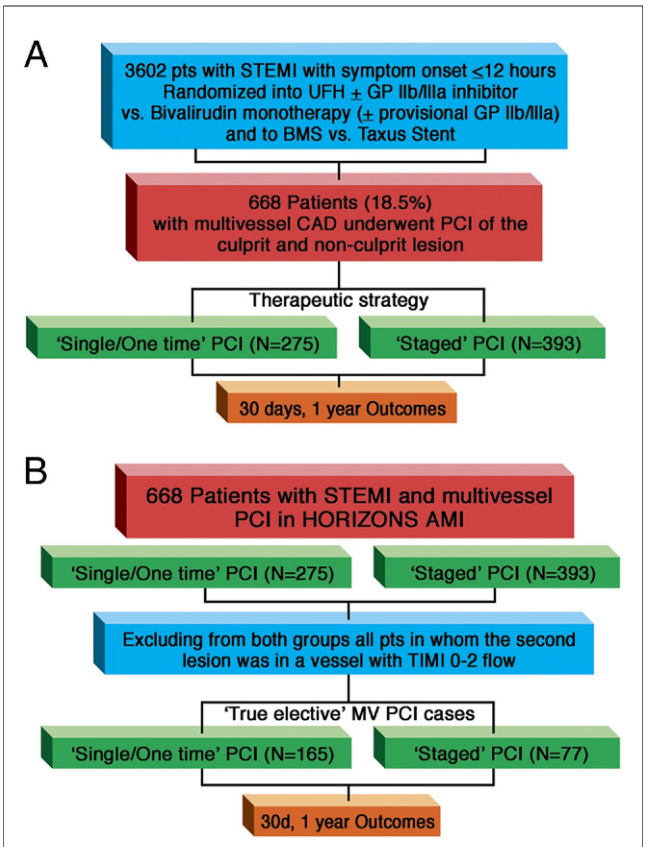

Figure 1 **Study Protocol**

(A) All patients undergoing multivessel primary coronary intervention (PCI) and **(B)** patients with true elective multivessel PCI in the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. BMS = bare-metal stent; CAD = coronary artery disease; GP = glycoprotein; MV = multivessel; pts = patients; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; UFH = unfractionated heparin.

with 1-time multivessel intervention and 77 patients with staged elective multivessel PCI (Fig. 1B).

Study endpoints. The study endpoints for the current analysis included the 1-year rates of major adverse cardiovascular event (MACE) and its components, consisting of death, reinfarction, ischemia-driven target vessel revascularization, and stroke. Stent thrombosis events were also adjudicated. Major bleeding (not related to coronary artery bypass graft surgery) and net adverse clinical events (NACE), defined as major bleeding or composite MACE, were additional pre-specified endpoints included in the original study and reported in the current analysis. The definitions of major bleeding and the individual component of MACE have been previously reported (4–6). Stent thrombosis was defined as the definite or probable occurrence of a stent-related thrombotic event, according to the Academic Research Consortium classification (7). An independent Clinical Events Committee blinded to treatment assignment adjudicated all primary endpoint and stent thrombosis events using original source documents.

Statistical methods. The present study represents a prespecified analysis from the HORIZONS-AMI trial. Categorical outcomes were compared by chi-square or Fisher's exact test. Continuous variables were compared by the Wilcoxon rank-sum test. The primary event analyses were performed using time-to-event data (for which patients were censored at the time of withdrawal from the study or at last follow-up), displayed using Kaplan-Meier methodology, and compared with the log-rank test. Cox proportional hazards regression was performed to determine the independent predictors of all-cause mortality at 30 days and 1 year. Variables were selected using a forward stepwise algorithm with entry and stay significance levels of 0.1.

Our multivariate model tested 2 analytical methods. First, we included in the multivariate model only selected covariates that are expected to be related to long-term outcomes. Then, to avoid an "over-fitting" problem due to relatively large number of variables and fewer outcome events, we used an additional propensity score model for each outcome category that tests single versus staged PCI using only the propensity score as a covariate. This covariate refers to a variable for the propensity to undergo multivessel intervention. It was developed using a logistic regression model and was aimed to reduce selection bias in the elected treatment strategy (i.e., single/deferred versus multivessel PCI strategy) and its potential impact on measured outcomes.

The propensity was adjusted for age, drug-eluting stent use, dyslipidemia, smoking history, prior coronary artery disease or peripheral vascular disease or stroke, Killip class ≥2, pre-randomization heparin treatment, and clopidogrel loading dose. Also, this method allowed us to reduce more effectively the number of covariates when outcome event counts were relatively low in our study. The elected variables that were included in the original model are listed as follows: age, sex, Killip class, anemia, creatinine clearance <60 ml/min, bivalirudin use (vs. unfractionated heparin plus GP IIb/IIIa), history of diabetes mellitus, clopidogrel loading dose (600 vs. 300 ng), pre-randomization heparin, symptom to first balloon time, left anterior descending artery disease, pre-TIMI flow grade, left ventricle ejection fraction (LVEF), and single vessel versus multivessel PCI.

Results

Patients and procedures. The median time interval between the first and second PCI procedures in the staged group was 30 days (range 6.0 to 51 days). The 2 groups were well matched (Table 1). The median baseline LVEF was not significantly different between groups, but more patients in the single PCI arm had a left ventricular ejection fraction ≤40% (20.5% vs. 11.1%, p = 0.002). Baseline medications were similar between groups (data not shown). Preintervention TIMI flow grade 0/1 in the culprit vessel was more prevalent in the staged PCI group (by both operator report and quantitative coronary angiography). The final angiographic culprit lesion rate of TIMI flow grade 3 was

Table 1 Baseline Characteristics, Procedures, and Medication Use

	Single PCI (n = 275)	Staged PCI (n = 393)	p Value
Mean age, yrs	62.0	63.5	0.84
Male, %	79.6	80.9	0.68
Diabetes mellitus, %	15.3	18.1	0.34
Hypertension, %	54.9	57.5	0.50
Hyperlipidemia, %	48.0	41.7	0.11
Smoking history, %	61.3	62.8	0.69
History of MI, %	9.5	7.9	0.47
History of angioplasty, %	11.3	7.9	0.14
History of bypass surgery, %	3.3	2.8	0.72
History of CHF	3.6	3.6	0.96
LAD culprit, %	40.6	35.1	0.09
Symptoms to balloon, min	232.0	229.0	0.94
Door to balloon, min	110.0	102.0	0.14
Killip class ≥2, %	10.6	7.1	0.11
Baseline LVEF, mean %	57.4	58.6	0.23
LVEF ≤40%, %	20.5	11.1	0.002
Pre-TIMI flow grade 0/1,*%	44.3	68.0	<0.0001
Pre-TIMI flow grade 0/1,†%	39.4	62.2	<0.0001
Post-TIMI flow grade 3,*%	93.2	92.4	0.63
Post-TIMI flow grade 3,*†%	91.7	86.7	0.02
Bivalirudin randomization, %	51.6	50.4	0.75
TAXUS stent randomization, %	81.5	72.3	0.009
Pre-randomization heparin, %	60.4	71.8	0.002
Received GPI,‡%	54.5	54.6	0.99
Aspiration catheter used, %	9.6	12.5	0.24
Thienopyridine loaded, %	99.3	99.7	0.57

*Operator report. †Quantitative coronary angiography core laboratory report. ‡Any glycoprotein IIb/IIIa administration during and after percutaneous coronary intervention (PCI).

CHF = congestive heart failure; GPI = glycoprotein IIb/IIIa inhibitor; LAD = left anterior descending artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

high (>90%) and similar between groups per operator report, but slightly less frequent in the staged PCI group per quantitative coronary angiography (86.7% vs. 91.7%, p = 0.02). Bivalirudin and GPI treatments were distributed equally among groups (Table 1). However, randomization to the TAXUS stent was more frequent in the single PCI group versus staged PCI group (81.5% vs. 72.3%, p = 0.009).

In the 1-time group as compared to the staged PCI group, the average number of stents implanted during the index procedure was higher (2.2 ± 1.1 vs. 1.7 ± 1.0, p < 0.0001), the number of vessels treated was greater (1.5 ± 0.5 vs. 1.0, p < 0.0001), the number of lesions treated was greater (1.7 ± 0.7 vs. 1.2 ± 0.5, p < 0.0001), the mean total stent length was greater (37 mm vs. 28 mm, p < 0.0001), a greater amount of contrast was utilized (275 ml vs. 235 ml, p < 0.0001), and the mean total fluoroscopy time was longer (16.0 min vs. 11.0 min, p < 0.0001).

Clinical outcomes. Table 2 summarizes the adverse events occurring through 1 year of follow-up for both groups. At 1 year, patients undergoing 1-time versus staged multivessel PCI had a significantly greater rate of all-cause mortality (9.2% vs. 2.3%, hazard ratio [HR]: 4.10, 95% confidence interval [CI]: 1.93 to 8.86, p < 0.0001) and cardiac mortality (6.2% vs. 2.0%, HR: 3.14, 95% CI: 1.35 to 7.27, p = 0.005). A higher mortality rate was present at 30 days after STEMI (all-cause mortality 5.8% vs. 1.5%, HR: 3.81, 95% CI: 1.51 to 9.62, p = 0.002; and cardiac mortality 5.5% vs. 1.5%; HR: 3.57, 95% CI: 1.40 to 9.09, p = 0.004). Time to mortality and cardiac mortality curves for patients with multivessel PCI, distinguished by revascularization strategy, are shown in Figure 2.

At 1 year, patients undergoing 1-time compared to staged PCI also experienced more stent thrombosis events, especially more "definite" stent thrombosis events within the first month after STEMI. There was no significant difference in the rate of reinfarction or target vessel revascularization between groups (Table 2). The composite MACE endpoint at 1 year (death, reinfarction, target vessel revascularization for ischemia, and stroke) tended to be higher in the 1-time PCI arm, although the overall difference did not reach statistical significance (18.1% vs. 13.4%, p = 0.08).

Major and minor bleeding complications rates were also significantly increased in the 1-time versus staged PCI groups according to some but not all of the definitions (Table 2). At 30 days, NACE was significantly higher among patients undergoing 1-time versus staged PCI (16.0% vs. 9.7%, HR: 1.72, 95% CI: 1.12 to 2.66, p = 0.01). However, the difference in NACE between groups was attenuated by 1 year so the difference was no longer significant (23.5% vs. 19.2%, HR: 1.29, 95% CI: 0.92 to 1.80, p = 0.14).

True elective procedures. After excluding patients in whom the nonculprit lesions were in vessels with TIMI flow grade 0 to 2, the 2 remaining groups (representing the "true" elective multivessel PCI groups) were again well matched for baseline features (data not shown), although the mean ejection fraction was lower in the 1-time PCI group (50% vs. 55%, p = 0.01). Patients undergoing elective 1-time multivessel PCI (n = 165) compared to a staged PCI strategy (n = 77) had higher 1-year rates of all-cause mortality (8.0% vs. 1.3%, p = 0.04) and cardiac mortality (4.9% vs. 0%, p = 0.05) (Fig. 3).

Multivariable analysis. The staged versus 1-time multivessel PCI strategy was independently associated with lower all-cause mortality at 30 days and at 1 year (Table 3). The finding of staged PCI being a predictor of reduced mortality persisted after adjusting the model for the observed covariable and also using the "propensity score" as the only covariable used in the second model (Table 3, lower part). Additional variables that also predicted mortality were Killip class ≥2 and measured creatinine clearance <60 ml/min.

Staged versus single PCI was also and independent predictor for improved MACE at 30 days and 1 year. Additional variable that were independently correlated with improved composite MACE are shown in Table 3. Finally, a strong similar trend for reduced mortality in favor of the staged PCI approach was also present in the true elective

Table 2 Adverse Events at 1 Year

	Single PCI (n = 275)	Staged PCI (n = 393)	RR (95% CI)	p Value
Mortality, all causes, %	9.2	2.3	4.10 (1.93–8.86)	<0.0001
Cardiac, %	6.2	2.0	3.14 (1.35–7.27)	0.005
Reinfarction (Q/non-Q)	6.5	4.7	1.43 (0.73–2.77)	0.29
Ischemic TVR, n	8.9	8.1	1.13 (0.66–1.93)	0.66
Stroke, total	0.4	0.8	0.51 (0.05–4.89)	0.55
Stent thrombosis, n/total n				
Definite	5.0	1.6	3.24 (1.23–8.54)	0.01
Probable	0.8	0.8	0.99 (0.16–5.90)	0.99
Definite or probable	5.7	2.3	2.49 (1.09–5.70)	0.02
Acute (0–24 h)	0.7	1.0	0.72 (0.13–3.88)	0.99
Acute/subacute (0–30 days)	4.8	1.8	2.66 (1.07–6.58)	0.03
Late (>30–365 days)	0.8	0.5	1.53 (0.22–10.9)	0.67
MACE	18.1	13.4	1.42 (0.96–2.1)	0.08
NACE	23.5	19.2	1.29 (0.92–1.80)	0.14
Bleeding endpoints				
Protocol major, non-CABG	9.5	6.9	1.38 (0.82–2.31)	0.22
Protocol major, all	9.5	7.1	1.33 (0.80–2.21)	0.23
Intracranial bleed	0	0	NA	NA
Blood transfusion	5.1	1.5	3.33 (1.30–8.57)	0.008
TIMI major	4.0	1.3	3.14 (1.10–8.95)	0.02
TIMI minor	2.5	5.1	0.50 (0.21–1.17)	0.10
TIMI major or minor	6.5	6.4	1.03 (0.57–1.85)	0.92
GUSTO LT* or severe	0.7	0.3	2.86 (0.26–1.36)	0.57
GUSTO moderate	4.4	1.3	3.43 (1.22–9.62)	0.01
GUSTO LT or severe or moderate	5.1	1.5	3.33 (1.30–8.57)	0.008

*Life-threatening (LT) stent thrombosis was defined according to the Academic Research Consortium classification.

CABG = cardiac artery bypass surgery; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries; MACE = major adverse cardiovascular events; NA = not applicable; NACE = net adverse clinical events; RR = relative risk; TVR = target vessel revascularization; other abbreviations as in Table 1.

PCI cohort at 1 year after STEMI event (HR: 0.15, 95% CI: 0.02 to 1.11, p = 0.06).

Discussion

Multivessel disease encountered during the course of STEMI PCI poses a therapeutic dilemma (8–16). It is also associated with an adverse prognosis among STEMI patients after primary PCI (8–16). Whether multivessel intervention during the index primary PCI procedure is safe has been the matter of debate. Some (10–12), but not all (8,13) studies have suggested that this practice is associated with increased mortality and reinfarction. More recently, advances in PCI techniques and adjunctive pharmacotherapy have led some operators and investigators to advocate a single-setting multivessel PCI strategy during the index STEMI procedure (8,9). The present analysis from the large-scale, contemporary and prospective international HORIZONS-AMI trial strongly suggests that a deferred angioplasty strategy for nonculprit lesions should remain the standard approach for patients with STEMI and multivessel disease undergoing primary PCI. Compared to a staged treatment approach, multivessel PCI that included nonculprit vessels during the acute STEMI reperfusion procedure was strongly associated with a greater hazard for 1-year all-cause mortality, cardiac mortality, MACE, and stent thrombosis. Even after multivariable correction for the baseline and post-procedure differences between the groups and also after using propensity score matching, staging the intervention remained a powerful independent predictor of enhanced survival. These findings also persisted after excluding all patients in whom the second nonculprit lesion was in a vessel with compromised angiographic epicardial flow, for which PCI was arguably "needed" during the index procedure. Thus, pending the results of a definitive randomized trial, a multivessel PCI strategy during the course of STEMI cannot be recommended as a routine approach in patients requiring multivessel intervention.

Our results are in accordance with the current American College of Cardiology/American Heart Association guidelines, which state that elective PCI should not be performed in a noninfarct-related artery at the time of primary PCI of the infarct-related artery in patients without hemodynamic compromise (Class IIIc indication) (2). Similarly, the European Cardiology Society guidelines state that in patients with multivessel disease, primary PCI should be directed only at the infarct-related artery; decisions about PCI on nonculprit lesions should be guided by objective evidence of residual ischemia at later follow-up (3). Notably, those recommendations were based on relatively small observa-

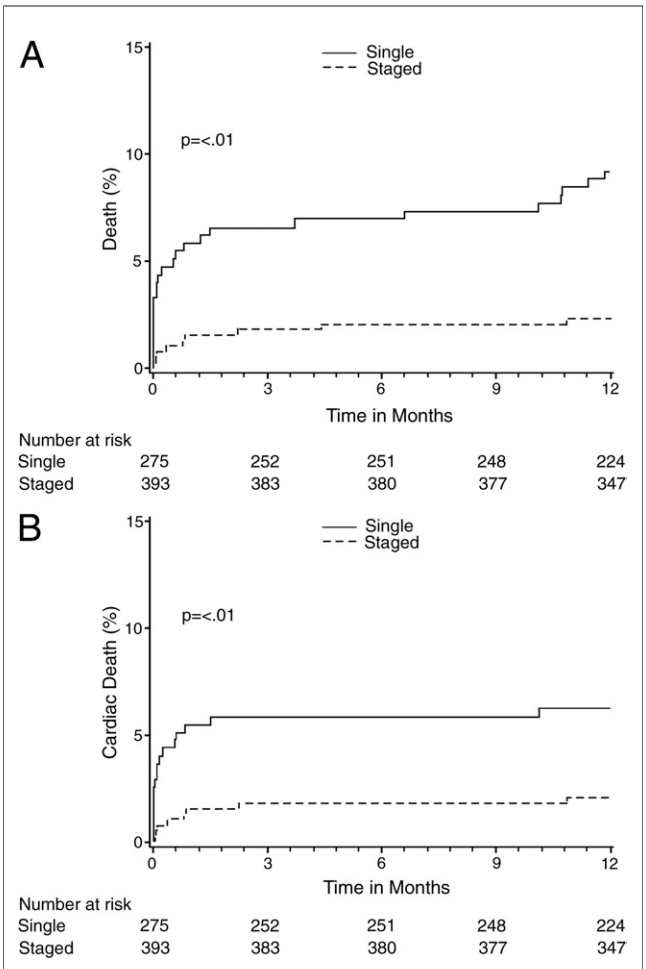

Figure 2 **Clinical Outcomes of Patients With Multivessel Disease**

One-year clinical outcomes of all patients with multivessel disease undergoing culprit and nonculprit lesion intervention according to 1-time **(solid lines)** versus staged **(dashed lines)** revascularization strategy. **(A)** Time to mortality. **(B)** Cardiac mortality.

tional studies. Thus, the present analysis from 1 of the largest PCI trials performed up to date provides important complementary and supportive data to the existing literature on which these guidelines are based.

The reasons why multivessel intervention during the index primary PCI procedure may not be safe are unknown, but are likely multifactorial. Any PCI procedure is challenging in the setting of hemodynamic instability and left ventricular dysfunction. The prothrombotic and inflammatory milieu in the early phase of STEMI may also increase procedural risks (17–19). Consistent with this mechanism, the incidence of stent thrombosis in the present study was increased in patients undergoing a single setting rather than staged multivessel intervention. Second, lesion severity in nonculprit vessels can be overestimated at the time of primary PCI because of diffuse coronary vasoconstriction and systemic endothelial dysfunction (20); rarely are noninvasive testing data available or the time taken to perform fractional flow reserve in this setting to guide multivessel intervention. Third, multivessel PCI increases contrast use, which may be less well tolerated in the patient with STEMI, especially if radiocontrast nephropathy develops (21). Finally, unforeseen periprocedural complications in the nonculprit vessel may be poorly tolerated due to the "double jeopardy" of large myocardial territories at risk (i.e., simultaneous impairment of the culprit and nonculprit regions).

Conversely, there are numerous reasons why multivessel PCI during the index procedure may be desirable. Plaque instability may not be limited to culprit lesions, and may result in recurrent ischemia and infarction (22). The SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) randomized trial demonstrated that the presence of silent ischemia after AMI is associated with a significantly higher rate of cardiac death and major adverse events if not treated (14). Complete coronary revascularization has been associated with a better long-term cardiac prognosis and

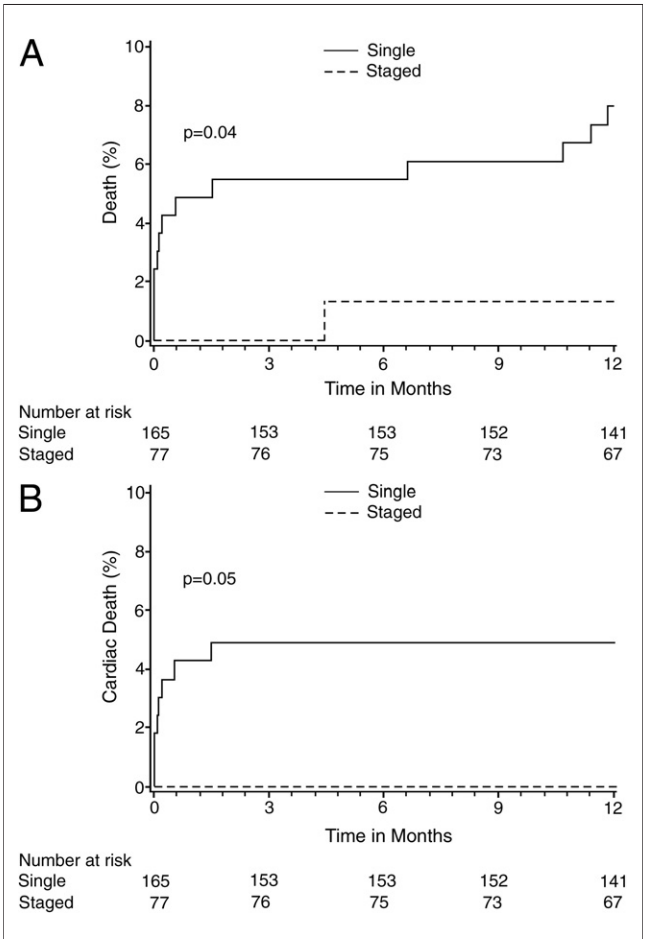

Figure 3 **Clinical Outcomes of True Elective PCI-Treated Patients**

One-year clinical outcomes among true elective multivessel primary coronary intervention (PCI)-treated patients according to 1-time **(solid lines)** versus staged **(dashed lines)** revascularization strategy. **(A)** Time to mortality. **(B)** Cardiac mortality.

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Table 3 Multivariable Predictors of 30-Day and 1-Year Mortality and MACE

	HR (95% CI)	p Value
Original model		
Predictors of mortality (30 days)		
Staged PCI (vs. single)	0.33 (0.11–0.94]	0.0388
Killip class ≥2	3.74 (1.27–11.03)	0.017
Creatinine clearance <60 ml/min	4.18 (1.54–11.33)	0.005
Predictors of mortality (1 yr)		
Staged PCI (vs. single)	0.30 (0.12–0.73)	0.0083
Killip class ≥2	3.02 (1.17–7.79)	0.022
Creatinine clearance <60 ml/min	4.91 (2.15–11.23)	0.0002
Predictors of MACE (30 days)		
Staged PCI (vs. single)	0.41 (0.19–0.89)	0.0248
Killip class ≥2	4.02 (1.67–9.69)	0.0019
Creatinine clearance <60 ml/min	2.13 (0.95–4.79)	0.0666
Baseline TIMI flow grade 0/1	4.12 (1.41–12.05)	0.0098
Predictors of MACE (1 yr)		
Staged PCI (vs. single)	0.53 (0.33–0.86)	0.01
History of diabetes mellitus	1.95 (1.12–3.37)	0.0173
Killip class ≥2	2.27 (1.17–4.38)	0.0148
Creatinine clearance <60 ml/min	1.79 (1.04–3.08)	0.0363
LAD disease	3.17 (1.15–8.75)	0.0262
Baseline TIMI flow grade 0/1	1.91 (1.10–3.30)	0.0212
LVEF (10% decrease)	1.24 (1.02–1.50)	0.03
Propensity score model		
Predictors of mortality (30 days)		
Staged PCI (vs. single)	0.31 (0.12–0.81)	0.0164
Propensity score	0.02 (0.00–0.86)	0.0416
Predictors of mortality (1 yr)		
Staged PCI (vs. single)	0.27 (0.13–0.60)	0.0011
Propensity score	0.04 (0.00–0.86)	0.0402
Predictors of MACE (30 days)		
Staged PCI (vs. single)	0.44 (0.23–0.84)	0.0127
Propensity score	0.05 (0.00–0.93)	0.0446
Predictors of MACE (1 yr)		
Staged PCI (vs. single)	0.71 (0.48–1.06)	0.0941
Propensity score	0.30 (0.05–1.96)	0.2082

HR = hazard ratio; other abbreviations as in Tables 1 and 2.

improved left ventricular function (13). Finally, the 1-time PCI strategy may be cost saving, and decrease the need for future hospitalizations and procedures. It is possible that the findings from the present and previous nonrandomized studies are due to selection bias and the presence of unmeasured confounders in the single-setting multivessel PCI group that necessitated earlier nonculprit intervention.

To address these issues, 2 small randomized trials have recently been performed. Politi et al. (23) assigned 214 STEMI patients with multivessel disease to culprit-lesion only PCI, 1-time multivessel PCI, or staged multivessel PCI treatment (23). In-hospital death, repeat revascularization, and rehospitalization occurred more frequently in the culprit-lesion angioplasty group (all $p < 0.05$). However, after a mean follow-up period of 2.5 years, there were no significant differences among the 3 groups in terms of death or MI. The HELP-AMI (Hepacoat for Culprit or Multivessel Stenting for Acute Myocardial Infarction) study was a small multicenter randomized study (n = 69) that performed an unbalanced randomization and compared culprit lesion treatment only (n = 17) to complete "1-time" multivessel PCI (n = 52) during STEMI (11). The study found the 1-time multivessel strategy was safe but not necessarily justified based on subsequent need for clinically driven revascularization procedures and/or economical considerations. However, both trials were under-powered for the endpoints examined. The APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) trial was designed to explore the incidence of and propensity for nonculprit interventions performed at the time of the primary PCI and its association with 90-day outcomes (24). Of the 5,373 patients who underwent primary PCI in this analysis, 2,201 had multivessel disease, and of those, only 217 (9.9%) underwent noninfarct-related arteries PCI. Ninety-day death and death/heart failure/shock were higher in the noninfarct-related group compared with the culprit only PCI group (12.5% vs. 5.6%, $p < 0.001$, and 17.4% vs. 12.0%, $p = 0.020$, respectively). After adjusting for patient and procedural characteristics as well as propensity for performing nonculprit PCI, this procedure remained independently associated with an increased hazard of 90-day mortality (adjusted HR: 2.44, $p < 0.001$). In addition, analysis of 1,598 patients enrolled in the EUROTRANSFER Registry database showed that in STEMI patients treated using emergent PCI, multivessel disease was identified as an independent predictor of 1-year death (25). In 70 patients (9%), nonculprit PCI was performed during the index PCI. These patients were at higher risk of 30-day and 1-year death compared to patients with culprit only PCI. However, this difference in mortality was no longer significant after adjustment for covariates.

Study limitations. In addition to the issue of residual confounding, several limitations of the present analysis warrant discussion: 1) although pre-specified, the present study is a retrospective nonrandomized subanalysis from a pivotal prospective randomized trial; 2) the cohort of 668 patients with STEMI undergoing multivessel PCI (41% during the index procedure) may still be under-powered to assess subtle distinctions between the 2 strategies; and 3) the specific reasons why operators chose a single procedure versus a staged approach was not prospectively collected. Despite our efforts to eliminate bias due to the nonrandomized nature of the comparison, we cannot totally refute the possibility that such bias actually existed and was not identified or eliminated in our careful statistical model. We have made our best attempt to reduce the impact of treatment bias by adding the propensity score covariate to the multivariate model. Although the event count was relatively low, findings remained with propensity score adjustment. Thus, the likelihood of a bias effect to explain our results is small.

Conclusions

These limitations notwithstanding, the results of the present study clearly suggest that a routine emergent multivessel PCI during the course of STEMI should be strongly discouraged. This is because it is associated with a greater hazard for subsequent mortality, stent thrombosis, and MACE in comparison to a staged PCI strategy. In the present analysis, we could not determine or compare the culprit vessel versus the nonculprit vessel PCI as this information has not been systematically recorded in the HORIZONS database. Thus, in summary, pending the results of a properly designed randomized trial, a deferred angioplasty strategy of nonculprit lesions should remain the standard approach to patients with STEMI and multivessel coronary artery disease.

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Key Words: angioplasty ■ coronary artery disease ■ myocardial infarction ■ stenting.