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Impact of Multiple Complex Plaques on Short-and Long-Term Clinical in Patients Presenting with ST-Segment Elevation Myocardial Infarction (From the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] Trial)

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Abstract

It is not known whether the extent and severity of non-culprit coronary lesions correlate with outcomes in patients with STEMI referred for primary PCI. We sought to quantify complex plaques in ST-segment elevation myocardial infarction (STEMI) patients referred for primary percutaneous coronary intervention (PCI) and to determine their effect on short- and long-term clinical outcomes by examining the core laboratory database for plaque analysis from the HORIZONS-AMI study. Baseline demographic, angiographic, and procedural details were compared between patients with single vs. multiple complex plaques undergoing single vessel PCI. Multivariable analysis was performed for predictors of long-term major adverse cardiac

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events (MACE), a combined end point of death, reinfarction, ischemic target vessel revascularization, or stroke, and for death alone. Single vessel PCI was performed in 3,137 patients (87%); 2,174 (69%) had multiple complex plaques and 963 (31%) had a single complex plaque. Compared to those with a single complex plaque, patients with multiple complex plaques were older ($p<0.0001$) and had more comorbidities. The presence of multiple complex plaques was an independent predictor of 3-year MACE (hazard ratio [HR]: 1.58; 95% confidence interval [CI]: 1.26–1.98, $p<0.0001$), and death alone (HR: 1.68; 95% CI: 1.05–2.70, $p=0.03$). In conclusion, multiple complex plaques are present in the majority of STEMI patients undergoing primary PCI and their presence is an independent predictor of short- and long-term MACE, including death. (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966)

Keywords

STEMI; PCI; multiple plaques

INTRODUCTION

Acute plaque rupture or erosion with subsequent thrombotic occlusion is the hallmark of ST-segment elevation myocardial infarction (STEMI) (1–2). Complex plaque morphology associated with the propensity for plaque disruption was thought to be present only in the infarct-related artery, but the identification of multiple complex plaques in STEMI patients has been reported in a small, single-center study (3). Our aim was to assess the prevalence of culprit and non-culprit complex plaques in a large group of STEMI patients undergoing primary percutaneous coronary intervention (PCI) in an era of contemporary medical therapy and interventional techniques and to determine their influence on short- and long-term clinical outcomes. To this end, we analyzed data from the large, prospective, randomized, multicenter Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial (4–5), which included detailed plaque analysis of the entire coronary tree.

METHODS

The HORIZONS-AMI trial evaluated bivalirudin (compared with heparin and glycoprotein receptor inhibitors) and, in a secondary randomization, drug-eluting stents (compared with bare metal stents) in STEMI patients undergoing primary PCI (4–5). All patients were pre-loaded in the emergency department with a thienopyridine prior to the procedure. Of the 3,602 patients randomized, quantitative and qualitative coronary angiographic analysis of all major epicardial coronary arteries was performed in 3,467 (96%) patients, and of these, PCI of a single coronary artery was performed in 3,137 (87%). These 3,137 patients form the basis of our study and were categorized as having single or multiple complex plaques. Patients with multivessel PCI were excluded to eliminate the confounding effect of treatment of multiple complex lesions beyond the infarct-related lesion. A single complex plaque was, by definition, the infarct-related lesion within the infarct-related artery. In patients who had multiple complex plaques the additional plaques were located at different

sites within the infarct-related artery (proximal or distal to the infarct-related lesion) or in a non-infarct-related artery. Non-infarct-related complex plaques were not treated at the time of the index procedure, even when located in the infarct-related artery.

Coronary angiograms were analyzed by a core angiographic laboratory (Cardiovascular Research Foundation, New York, New York) and detailed quantitative and qualitative coronary angiography (6) was performed on all major epicardial coronary arteries. A pre-specified definition for complex plaque defined as a lesion that had >50% diameter stenosis with at least 2 of the following: presence of a filling defect or thrombus, ulceration, irregularity, Thrombolysis in Myocardial Infarction (TIMI) <3 flow, moderate or severe calcification, or involvement of a bifurcation was used by the core angiographic laboratory. Multiple complex plaques within the same vessel were determined to be “multiple” when they were located in a different segment separated by ≥5mm of normal appearing vessel.

Outcomes including death, cardiac death, reinfarction, stroke, and major bleeding (HORIZONS-AMI definition, which includes intracranial, intraocular, or retroperitoneal bleeding, access site bleeding requiring intervention or surgery, hematoma >5 cm, any blood product transfusion, reoperation for bleeding, or decrease in hemoglobin of >3 g/dL with and ≥4 g/dL without overt source of bleeding) were independently adjudicated by a committee blinded to study allocation. In addition, major adverse clinical events (MACE), a combined end point of death, reinfarction, ischemia/clinically-driven target-vessel revascularization, or stroke and net adverse clinical events (NACE), the combined end point of MACE or non-coronary artery bypass graft (CABG) related major bleeding were analyzed for those with single vs. multiple complex plaques. Clinical follow-up was obtained at hospital discharge, at 30 days, and at 1, 2, and 3 years.

Baseline categorical variables are summarized as counts and percentages and were compared using chi-square testing or Fisher exact test, as appropriate; continuous variables are summarized as medians with interquartile range (IQR) and were compared using Mann-Whitney *U* test. Multivariable analysis adjusting for age, gender, race, diabetes, hypertension, prior myocardial infarction, prior CABG, history of congestive heart failure, baseline creatinine clearance, left ventricular ejection fraction <40%, treatment with balloon angioplasty only, and time to reperfusion as covariates was performed to determine the predictors of MACE and death alone. A 2-tailed *p* value of <0.05 was considered significant. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

Of the 3,137 subjects, 963 (31%) had a single complex plaque (the infarct-related lesion), and 2,174 (69%) had multiple complex plaques. Of the patients with multiple plaques, 809 (26%) had 2, 533 (17%) had 3, 358 (11%) had 4 and 474 (15%) had 5 complex plaques. The demographic and baseline characteristics of the two groups are shown in Table 1. Patients with multiple complex plaques had more comorbidities, higher rates of baseline medication use, were less likely to undergo primary PCI (95.4% vs. 97.6%, *p*=0.003), and more likely to be referred for CABG (2.7% vs. 0.3%, *p*<0.0001). Moreover, those with multiple complex plaques had longer symptom onset to presentation (118 [65.0, 210.0] minutes vs. 107 [60.0,

190.0] minutes, $p=0.036$), and longer door-to-balloon times (100 [73.0, 135.0] minutes vs. 93 [69.0, 130.0] minutes, $p=0.007$).

The angiographic and procedural details of the two groups are shown in Table 2. Patients with multiple complex plaques had worse left ventricular ejection fraction, more extensive coronary artery disease, lower rates of TIMI 3 flow before PCI, and worse infarct artery reperfusion as demonstrated by higher final corrected TIMI frame counts and lower rates of final myocardial blush grade 3. In patients with multiple complex plaques, the majority of plaques (79%) were located in a non-culprit artery.

Clinical outcomes at 30 days and 3 years are shown in Table 3. At 3-year follow-up, patients with multiple complex plaques had significantly higher rates of MACE, all-cause death, cardiac death, and bleeding. Rates of reinfarction alone, however, were not significantly different between patients with single and multiple complex plaques. On multivariable analysis, the presence of multiple complex plaques was a significant independent predictor of MACE at 3 years (hazard ratio: 1.58, 95% confidence interval: 1.26–1.98, $p<0.0001$), together with a history of congestive heart failure, diabetes mellitus, prior myocardial infarction, depressed ejection fraction, worse kidney function, non-Caucasian race, and balloon angioplasty without stenting (Figure 1). The presence of multiple complex plaques was also a significant independent predictor of death alone at 3 years (hazard ratio: 1.68, 95% confidence interval: 1.05–2.70, $p=0.03$), together with history of congestive heart failure, diabetes, prior myocardial infarction, depressed ejection fraction, and worse kidney function (Figure 2). There was a stepwise increase in MACE and death alone with increasing numbers of complex plaques. At 3-year follow-up, MACE doubled from 14.4% in patients with a single complex plaque, to 29.5% in patients with 5 complex plaques (Figure 3). Similarly, death tripled from 3.6% in patients with a single complex plaque, to 10.0% in patients with 5 complex plaques (Figure 4).

DISCUSSION

The 3 major findings of this study are that multiple complex plaques are present in most (69%) STEMI patients, there is a stepwise increase in both MACE and death alone with increasing numbers of complex plaques, and that their presence, despite use of contemporary medical therapy and interventional techniques, is an independent predictor of long-term adverse clinical events, including death. We propose that the presence of multiple complex plaques should be factored into clinical risk-assessment tools for STEMI patients and that future studies should focus on developing novel strategies to address not only culprit, but also non-culprit plaques in order to improve outcomes in STEMI patients with more extensive coronary artery disease.

Our findings confirm, in a larger cohort of STEMI patients, a prior observation that multiple complex plaques are associated with adverse short- and long-term clinical outcomes (3). It is striking that despite recent advances in both medical therapy and percutaneous techniques, clinical outcomes in STEMI patients with multiple complex plaques remain poor and increasing numbers are associated with a worse prognosis. Our findings not only underscore the high prevalence of multiple complex plaques in STEMI patients but also suggest that

this readily obtainable angiographic parameter may improve the predictive accuracy of the risk assessment scores already available (7,8) by adding a qualitative dimension to the quantitative measure of diameter % stenosis.

The hypothesis that plaque instability is not a local occurrence but rather the consequence of a systemic process that disrupts plaques throughout the coronary tree has been previously described (3,9,10). In support of this contention, investigators in one study performed coronary angiography of all three coronary arteries one month following successful fibrinolysis or primary PCI for STEMI: yellow (vulnerable) plaques were equally prevalent in culprit and non-culprit coronary arteries (11). More recently, the same investigators used angiography to assess the frequency of plaque disruption (plaque with evidence of thrombus) in non-culprit segments of the culprit artery in STEMI patients immediately after reperfusion, and at 1 and 6 months (12). Nearly one-third of patients with STEMI had evidence of disrupted plaques in non-culprit segments of the infarct-related artery, and at 6-months these areas showed signs of healing similar to the culprit segments (12). However, in another angiographic study of patients undergoing primary PCI for STEMI investigators found that 82% of the non-culprit complex plaques identified on the index angiogram remained complex on follow-up angiography (mean follow-up duration, 192 $\pm$ 33 days) (13). Together, these studies point to the fact that vulnerable plaques distinct from the infarct lesion are common and undergo changes during the acute process, which may or may not heal over time, enhancing their potential to cause future thrombotic events. In another study supporting the role for systemic factors (14) investigators showed that coronary flow in STEMI patients was slower than normal in the non-infarct-related arteries and patients who died had significantly slower global flow than patients who survived. Using coronary angiographic findings for risk assessment post-STEMI, however, must be viewed in the context of landmark studies that have shown that angiography significantly underestimates the extent of coronary artery disease seen at necropsy (15,16), and that the severity of disease seen angiographically does not predict whether the lesion will progress to an acute thrombotic occlusion (17,18).

The results of our study provide a potential mechanistic insight into the recent observation of the Randomized Trial of Preventive Angioplasty in Myocardial Infarction (PRAMI) trial, which showed that in subjects undergoing PCI for STEMI, preventive PCI of non-infarct-related coronary arteries was associated with improved clinical outcomes (19). We posit that the majority of the non-infarct-related artery lesions were likely complex in nature, and the mechanism for the observed improved outcomes was reduction in thrombotic events associated with these lesions.

Our study has limitations. First, in the HORIZONS-AMI study, the infarct-related artery was not specified in the case-report form. However, we only included patients who underwent PCI of a single vessel at the index procedure, thus eliminating the chance that a given patient had a thrombotic occlusion of more than one epicardial vessel or that a vessel other than the infarct-vessel was treated. Second, while more complex plaques may have been present and could have been identified by more advanced imaging such as intravascular ultrasound or optical coherence tomography, our study used core laboratory-based analysis techniques that are routinely used in clinical practice. In the future, however, non-invasive cardiac testing

may be instrumental in more fully delineating the functional significance of non-culprit complex plaques identified on angiography. Third, the HORIZONS-AMI study used a pre-specified definition for complex plaque that included the presence of calcification and involvement of a bifurcation which may be, at least in part, why multiple complex plaques were not a predictive of reinfarction. Finally, we could not determine whether or not the clinical events noted in follow-up were linked to the untreated complex plaques or not.

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Figure 1.

Forest Plot for Multivariate Cox Models for 3-Year MACE

CHF = congestive heart failure, CI = confidence interval; LVEF = left ventricular ejection fraction, MACE = major adverse cardiac events (a composite endpoint of death, MI, ischemic target vessel revascularization, or stroke); MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty.

Figure 2.

Forest Plot for Multivariate Cox Models for 3-Year Death

CHF = congestive heart failure; CI = confidence interval; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Figure 3.

Kaplan-Meier Survival Curve for 3-Year MACE According to the Number of Complex Plaques
 MACE = major adverse cardiac events (a composite endpoint of death, MI, ischemic TVR, or stroke).

Figure 4.
Kaplan-Meier Survival Curve for 3-Year Death According to the Number of Complex Plaques

Table 1

Demographic and Baseline Characteristics

Variable	Single Complex Plaque (n = 963)	Multiple Complex Plaques (n = 2,174)	p Value
Age, (yrs)	57.2 (49.4, 65.7)	61.8 (54.1, 71.0)	<0.0001
Male	73.9% (712/963)	78.1% (1,698/2,174)	0.011
Body mass index, (kg/m ²)	26.8 (24.3, 30.1)	27.3 (24.7, 30.3)	0.057
Hypertension *	46.9% (452/963)	55.7% (1,210/2,172)	<0.0001
Hyperlipidemia [†]	40.5% (390/963)	43.8% (952/2,172)	0.082
Current smoker	53.9% (516/958)	43.9% (948/2,161)	<0.0001
Diabetes mellitus	11.8% (114/963)	19.0% (413/2,172)	<0.0001
Prior myocardial infarction	6.6% (64/963)	13.4% (290/2,172)	<0.0001
Prior percutaneous coronary intervention	8.7% (84/963)	12.0% (261/2,171)	0.007
Prior coronary bypass	0.5% (5/963)	4.0% (86/2,172)	<0.0001
Prior angina pectoris	19.0% (183/963)	22.4% (486/2,171)	0.033
Heart failure	1.9% (18/963)	3.2% (70/2,172)	0.034
Ventricular arrhythmias	1.3% (13/963)	0.6% (13/2,172)	0.032
Peripheral vascular disease	3.4% (33/963)	4.7% (103/2,171)	0.095
Renal insufficiency	2.3% (22/963)	3.2% (69/2,171)	0.169
Baseline medications			
Aspirin	19.4% (187/963)	25.6% (554/2168)	0.0002
Thienopyridines	2.0% (19/963)	3.4% (73/2174)	0.034
Beta-blocker	17.4% (168/963)	23.2% (503/2168)	0.0003
Calcium channel blocker	8.4% (81/963)	11.5% (250/2168)	0.009
ACE/ARB	20.4% (196/963)	25.6% (555/2168)	0.002
Insulin	3.4% (33/963)	4.5% (97/2168)	0.175
Oral hypoglycemic	7.3% (70/963)	11.7% (253/2167)	0.0002
Diuretic	9.4% (91/963)	11.9% (258/2168)	0.044
Symptom onset to presentation (min)	107.0 (60.0, 190.0)	118.0 (65.0, 210.0)	0.036
Door-to-balloon time (min)	93.0 (69.0, 130.0)	100.0 (73.0, 135.0)	0.007
Primary percutaneous coronary intervention	97.6% (940/963)	95.4% (2,073/2,174)	0.003
Coronary bypass without PCI	0.3% (3/963)	2.7% (59/2,174)	<0.0001

Values are median (IQR) or percent (%).

ACE= angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; PCI= percutaneous coronary intervention.

* patients treated with antihypertensive medication, and untreated patients with known systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg

[†] patients with total cholesterol level >200 mg/dl, or current use of lipid-lowering drugs

Table 2**Angiographic and Procedural Details**

Variable	Single Complex Plaque (n = 963)	Multiple Complex Plaques (n = 2,174)	p Value
Randomized to Bivalirudin	50.2% (484/964)	49.3% (1078/2187)	0.636
Randomized to UFH + GP IIb/IIIa	49.8% (480/964)	50.7% (1109/2187)	0.636
LVEF <40%	11.6% (97/838)	15.7% (286/1,818)	0.005
Extent of coronary artery disease			<0.0001
1-vessel disease	99.9% (962/963)	20.9% (455/2,174)	
2-vessel disease	0.0% (0/963)	48.5% (1,054/2,174)	
3-vessel disease	0.0% (0/963)	30.4% (660/2,174)	
1 total occlusion	57.9% (558/963)	66.0% (1,434/2,174)	<0.0001
Length of disease (mm)/patient	26.42 ± 17.05 (880)	52.47 ± 29.34 (2,171)	<0.0001
Total number of stents/patient	1.3 ± 0.6 (913)	1.5 ± 0.8 (1956)	<0.0001
Total stent length (mm)/patient	24.0 [16.0, 28.0] (895)	24.0 [20.0–36.0] (1916)	<0.0001
Any aspiration device	12.6% (117/932)	11.4% (234/2046)	0.381
Any thrombectomy device	1.0% (9/925)	1.1% (23/2042)	0.708
Drug-eluting stent	70.7% (622/880)	76.3% (1404/1839)	0.002
Bare metal stent	29.3% (258/880)	23.7% (435/1839)	0.002
Pre-PCI TIMI 3 flow in IRA	25.5% (240/940)	20.8% (426/2,051)	0.004
Final TIMI 3 flow in IRA	87.1% (817/938)	85.1% (1743/2,047)	0.166
Pre-PCI cTFC in IRA	26.0 (18.0, 38.0)	30.0 (20.0, 44.0)	0.001
Final cTFC in IRA	20.0 (14.0, 28.0)	21.0 (15.0, 30.0)	0.001
Pre-PCI MBG 3 in IRA	4.9% (46/939)	3.8% (78/2,037)	0.175
Final MBG 3 in IRA	55.5% (520/937)	48.6% (989/2,033)	0.0005

Values are median [IQR], mean ± SD, or percent (%).

cTFC = corrected TIMI frame count; GP = glycoprotein; IRA = infarct-related artery; LVEF = left ventricular ejection fraction; MBG = myocardial blush grade; PCI = percutaneous coronary intervention; TIMI = Thrombolysis in Myocardial Infarction; UFH = unfractionated heparin.

Table 3

Clinical Outcomes

Variable	Single Complex Plaque (n = 963)	Multiple Complex Plaques (n = 2,174)	p Value
30-Day			
Net adverse clinical events *	9.8% (94/963)	11.4% (247/2,174)	0.190
Major adverse cardiac events	3.5% (34/963)	5.8% (126/2,174)	0.008
Death	1.2% (12/963)	2.8% (61/2,174)	0.008
Cardiac death	1.1% (11/963)	2.5% (54/2,174)	0.015
Reinfarction	1.4% (13/963)	1.8% (38/2,174)	0.407
Death or reinfarction	2.5% (24/963)	4.3% (94/2,174)	0.013
Stroke	0.4% (4/963)	0.7% (16/2,174)	0.295
TVR	1.9% (18/963)	2.5% (54/2,174)	0.282
HORIZONS major bleeding [†]	7.9% (76/963)	10.3% (223/2,174)	0.039
TIMI major bleeding	2.8% (27/963)	5.1% (111/2,174)	0.004
GUSTO severe bleeding	0.5% (5/963)	0.6% (127/2,174)	0.002
3-year			
Net adverse clinical events *	20.7% (196/963)	28.6% (609/2,174)	<0.0001
Major adverse cardiac events	14.4% (135/963)	24.6% (520/2,174)	<0.0001
Death	3.6% (34/963)	7.6% (161/2,174)	<0.0001
Cardiac death	1.8% (17/963)	4.5% (95/2,174)	0.0003
Reinfarction	5.6% (52/963)	7.7% (156/2,174)	0.051
Death or reinfarction	8.8% (83/963)	14.2% (299/2,174)	<0.0001
Stroke	1.0% (9/963)	2.2% (45/2,174)	0.021
TVR	10.0% (92/963)	15.4% (315/2,174)	<0.0001
HORIZONS major bleeding [†]	9.4% (90/963)	11.7% (251/2,174)	0.066
TIMI major bleeding	3.4% (32/963)	5.9% (127/2,174)	0.003
GUSTO severe bleeding	0.7% (7/963)	1.0% (20/2,174)	0.571

Values are percent (%).

* Death, myocardial infarction, ischemia-driven TVR, stroke, or major bleeding (non-coronary artery bypass grafting);

[†] including coronary artery bypass grafting-related.

GUSTO = Global Utilization of Streptokinase To open Occluded arteries, TIMI = Thrombolysis in Myocardial Infarction; TVR = target vessel revascularization.