Impact of bifurcation target lesion on angiographic, electrocardiographic, and clinical outcomes of patients undergoing primary percutaneous coronary intervention (from the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction [HORIZONS-AMI] trial)

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KEYWORDS

- bifurcation lesion
- percutaneous coronary intervention
- ST-segment elevation myocardial infarction

Abstract

Aims: Using the database from the large-scale, prospective, randomised HORIZONS-AMI trial, the authors sought to assess the impact of bifurcation target lesions (BTL) on angiographic, electrocardiographic, and clinical outcomes in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).

Methods and results: In HORIZONS-AMI, bifurcation lesions in which a provisional approach was planned were eligible for enrolment. By angiographic core laboratory assessment of 3,306 patients with STEMI undergoing primary PCI, 333 patients (10%) had ≥1 BTL, and 2,973 patients had no BTL. There were no significant differences in baseline characteristics between the groups, except for lower left ventricular ejection fraction and more frequent left anterior descending infarct artery in the BTL group. BTLs required longer procedural and fluoroscopy times and higher contrast loads, but rates of TIMI 3 flow post PCI were similar in both groups (with vs. without BTL 99% vs. 87%, p=0.25). ST-segment resolution ≥70% by core laboratory analysis was similar in both groups (48% vs. 50%, p=0.47). Importantly, there was no difference between groups in the rate of death (6.1% vs. 6.7%, p=0.72), definite or probable stent thrombosis (4.2% vs. 5.2%, p=0.42), and ischaemic target vessel revascularisation (14.3% vs. 14.0%, p=0.86) during three-year follow-up.

Conclusions: Although the PCI procedure involving BTL was more complex, the acute results and late outcomes in patients with BTLs were comparable to those in patients without BTLs.

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Introduction

The development of atherosclerosis in or next to coronary bifurcations is relatively frequent such that 15-20% of patients undergoing a percutaneous coronary intervention (PCI) have a bifurcation target lesion (BTL). PCI involving BTL remains a challenge for interventional cardiologists. Such procedures are technically complex and are often associated with a higher restenosis rate and worse clinical outcomes[1-3].

Data on long-term outcomes of BTLs in ST-segment elevation myocardial infarction (STEMI) after primary PCI are limited. We therefore analysed data from the large-scale, prospective, randomised Harmonising Outcomes With Revascularisation and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial to assess the impact of BTL on angiographic, electrocardiographic, and clinical outcomes in patients with STEMI undergoing primary PCI.

Methods

The HORIZONS-AMI trial was a prospective, open-label, randomised, multicentre trial in patients with STEMI undergoing primary PCI. The study protocol was approved by the institutional review board or ethics committee at each centre, and written informed consent was obtained from all patients. The study design and results have been previously described[4-7]. Briefly, a total of 3,602 consecutive STEMI patients (≥18 years of age, <12 hours from symptom onset) were enrolled. Patients were randomised 1:1 to either a combination of unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (abciximab or eptifibatide) or bivalirudin alone. Aspirin and a clopidogrel loading dose (300 mg or 600 mg) were administered prior to catheterisation. After patency was restored in the infarct-related artery, selected patients eligible for stenting were randomised in 3:1 fashion to either a paclitaxel-eluting stent (TAXUS® Express™; Boston Scientific, Natick, MA, USA) or an otherwise identical bare metal (Express™; Boston Scientific) stent. For the purposes of the present pre-specified analysis, data on 3,306 patients with ≥1 significantly stenosed epicardial coronary artery undergoing primary PCI were divided into two groups according to the presence or absence of ≥1 BTL based on core laboratory angiographic assessment. Of note, a single-stent strategy was required for all of these BTLs, with provisional use of a second stent in the side branch allowed for suboptimal results. Patients with BTL in whom a definite two-stent strategy was required (n=37) were excluded from enrolment in HORIZONS-AMI.

The primary endpoints for the HORIZONS-AMI trial were: 1) major adverse cardiovascular events (MACE; death from any cause, stroke, reinfarction and unplanned revascularisation for ischaemia) and 2) major bleeding unrelated to coronary artery bypass grafting (CABG). Net adverse cardiovascular event (NACE) was defined as the occurrence of MACE or major bleeding unrelated to CABG. The definitions of endpoint components have previously been reported[4-7]. Patients were followed for three years. For the purpose of the present analysis three-year mortality, definite/probable stent thrombosis, and ischaemic target vessel revascularisation were selected as primary outcome measures. All primary endpoint events were adjudicated by an independent

clinical events committee blinded to treatment assignment, using original source documents.

Quantitative and qualitative coronary analysis was performed using standard definitions. Infarct artery flow was characterised by the thrombolysis in myocardial infarction (TIMI) classification[8]. Myocardial blush grade (MBG) was assessed according to the densitometric method, which evaluates the maximal intensity of contrast penetrating the infarct zone in comparison to unaffected territories[9].

The sum of ST-segment elevation was measured with lens-intensified calipers to the nearest 0.025 mV, 20 ms after the end of the QRS complex from leads I, aVL and V1 to V6 for anterior myocardial infarction and leads II, III, aVF, V5 and V6 for inferior myocardial infarction. Complete resolution was defined as ≥70% resolution of the initial sum of ST-segment elevation[10].

Differences in categorical variables were analysed using the chi-square test or Fisher's exact test, as appropriate. Continuous data are presented as medians (interquartile range) and were compared using the Wilcoxon rank sum test. The difference in the rates of death, definite/probable stent thrombosis, and ischaemic target vessel revascularisation between groups during the three-year follow-up period was assessed by the Kaplan-Meier method using the log-rank test. Additionally, the relationship between presence of BTL and clinical outcomes was examined with the use of both unadjusted and multivariable-adjusted Cox proportional hazards models. The first Cox model made no statistical adjustments for any covariates. The second model included the following covariates: baseline characteristics and demographics (age, sex, race, body mass index, hypertension, hyperlipidaemia, smoking, diabetes mellitus, insulin-dependent diabetes mellitus, previous myocardial infarction, previous coronary bypass grafting, previous angina, previous congestive heart failure, history of peripheral vascular disease, white cell blood count, baseline Killip class 1, baseline thrombocytopenia, baseline anaemia, creatinine clearance, left ventricular ejection fraction, symptoms onset to first balloon inflation time), pharmacotherapy (randomisation: bivalirudin vs. unfractionated heparin plus glycoprotein IIb/IIIa inhibitor, clopidogrel loading dose, pre-randomisation heparin, baseline aspirin, baseline thienopyridine), and angiographic parameters (left anterior descending artery disease, baseline TIMI flow, baseline reference vessel diameter, presence of thrombus, vessel ulceration, aneurysm, calcification, number of lesions treated, number of vessels treated, lesion length, final TIMI 3 flow). All tests were two-tailed, and a p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Of 3,306 patients enrolled in the study, 333 patients (10%) had ≥1 BTL and 2,973 (90%) did not. Baseline characteristics of the patient population according to the presence of BTL are shown in **Table 1**. There were no significant differences in baseline characteristics between groups, except for a higher prevalence of left ventricular ejection fraction <40%, a shorter time from symptom onset to hospital arrival, and less frequent presence of diabetes mellitus treated with insulin in the BTL group.

Table 1. Baseline characteristics, treatment and clinical status on admission stratified by presence of bifurcation target lesion.

Variable	≥1 Bifurcation target lesion (n=333)	No bifurcation target lesion (n=2,973)	*p*-value
Age (yr)	59.9 [53.4, 70.0]	60.1 [52.4, 69.6]	0.62
Male (%)	81.1	76.7	0.07
Body mass index (kg/m²)	27.2 [24.8, 30.1]	27.1 [24.5, 30.2]	0.73
Arterial hypertension (%)	49.5	53.0	0.24
Hyperlipidaemia (%)	42.6	42.7	0.98
Diabetes mellitus (%)	15.6	16.3	0.75
Insulin (%)	2.1	4.6	0.03
Previous angina (%)	23.7	21.8	0.42
Previous myocardial infarction (%)	10.5	10.5	0.99
Previous heart failure symptoms (%)	2.4	2.7	0.76
Previous percutaneous coronary intervention (%)	11.7	10.4	0.45
Previous coronary artery bypass grafting (%)	2.1	2.6	0.57
Current smoker (%)	42.2	47.5	0.06
Peripheral arterial disease (%)	3.6	4.4	0.49
History of renal insufficiency (%)	1.8	2.9	0.24
Creatinine clearance (mL/min)	88.2 [69.8, 111.2]	88.8 [67.9, 113.9]	0.97
Anaemia* (%)	10.8	10.4	0.81
Major cardiac rhythm/rate disturbances	2.1	3.0	0.37
Left ventricular ejection fraction <40% (%)	20.9	13.9	0.002
Killip class 2-4 on admission (%)	10.5	8.5	0.21
Symptom onset to emergency unit (min)	107 [65, 226]	130.0 [76, 235]	0.02
* Anaemia is defined as baseline haematocrit <39 for males and <36 for females			

As shown in **Table 2**, the left anterior descending artery was the infarct-related artery significantly more frequently in patients with BTL. Overall ischaemic time was similar in the two groups. BTLs were treated with mean 1.6±0.8 stents, not different from the non-BTL group. Primary PCI within BTL required longer procedural and fluoroscopy times and higher contrast load, but rates of TIMI 3 flow post PCI were similar in both groups. There was no difference in the rate of final MBG 2/3 after primary PCI between groups (78% vs. 76%, p=0.37).

Complete (≥70%) ST-segment resolution 60 minutes after primary PCI by electrocardiographic core laboratory analysis was similar between the two groups (with vs. without BTL, 48% vs. 50%, p=0.47). As confirmed by both unadjusted and multivariable-adjusted Cox proportional hazards models, there were no significant differences in clinical outcomes during the three-year follow-up period in patients with vs. without BTL (**Table 3** and **Figure 1**). There was no difference in all-cause mortality at 30 days (with vs. without BTL 1.2% vs. 2.5%, p=0.13) or between 30 days and three years (5.0% vs. 4.3%, respectively, p=0.48). Overall three-year mortality did not differ between groups **(Table 3)**.

There were 192 patients (60%) with BTL treated with one stent and 129 patients (40%) with BTL treated with >1 stent. At 30 days, there were no differences in the rates of all-cause mortality (1 vs. >1 stent implanted 0% vs. 1.6%, p=0.08), definite/probable stent thrombosis (1.6% vs. 1.6%, p=1), or the rate of ischaemic target vessel revascularisation (1.6% vs. 1.6%, p=1). At three years there were still no significant differences in the rates of all-cause death in BTL patients with 1 vs. >1 stent implanted (5.3% vs. 6.3%, p=0.69), definite/probable stent thrombosis (3.8% vs. 4.9%, p=0.64), or ischaemic target vessel revascularisation (11% vs. 18%, p=0.10).

Discussion

This is the largest study to date specifically assessing the impact of BTL presence on outcomes of patients undergoing primary PCI for STEMI. In contrast to the results from prior series of patients undergoing elective PCI, primary PCI of BTL in the present large-scale STEMI study was associated with outcomes comparable to those observed in patients undergoing non-BTL primary PCI.

The impact of BTL on primary PCI outcomes was previously assessed in two studies. Abdel-Hakim et al[11] reported the outcomes of 646 patients undergoing primary PCI from a single-centre database. BTL were found in 23% of patients and the provisional T-stenting technique was used in the majority of cases (89%). The frequency of TIMI 3 flow after PCI was 92% for BTL compared with 93% for non-BTL (p=0.65). There were no differences in the in-hospital (13% vs. 11%, p=0.72) or one-year MACE rates (23% vs. 20%, p=0.56)[11]. Frangos et al[12] reported data from 114 patients with BTL and 114 patients without BTL, matched according to age,

Table 2. Procedural details stratified by presence of bifurcation target lesion.

Variable		≥1 Bifurcation target lesion (n=333)	No bifurcation target lesion (n=2,973)	*p*-value
Clopidogrel 300 mg (%)		38.5	34.3	0.13
Clopidogrel 600 mg (%)		59.9	64.5	0.10
Abciximab (%)		24.6	30.3	0.03
Eptifibatide (%)		28.8	25.9	0.25
Bivalirudin (%)		51.4	49.7	0.57
Diagnostic catheterisation	Femoral artery access (%)	95.8	93.5	0.10
	Radial artery access (%)	4.2	6.2	0.15
Symptom onset to first balloon inflation (min)		214 [153, 335]	223 [161, 333]	0.36
One or more stents implanted (%)		96.4	94.3	0.11
Number of stents implanted (%)		1.6±0.8	1.5±0.8	0.29
Any study TAXUS stent (%)		69.5	69.1	0.89
Any study Express stent (%)		19.3	24.7	0.03
Total stent length implanted (mm)		24 [20, 36]	24.0 [20, 40]	0.02
Total fluoroscopy time (min)		16 [10, 23]	11 [7, 16]	<0.0001
Total amount of contrast (mL)		260 [203, 335]	220 [176, 290]	0.01
Time from first to last angiogram (min)		50 [38, 73]	40 [29, 57]	<0.0001
Any aspiration catheter (%)		11.1	11.6	0.80
Infarct-related artery	Left anterior descending (%)	55.3	38.8	<0.0001
	Left circumflex (%)	25.5	14.7	<0.0001
	Right (%)	17.9	44.8	<0.0001
	Left main (%)	1.3	0.4	0.04
	Saphenous vein graft (%)	0.0	1.1	0.04
TIMI flow pre percutaneous coronary intervention	TIMI 0/1 flow (%)	60.5	60.3	0.95
	TIMI 2 flow (%)	16.7	13.4	0.08
	TIMI 3 flow (%)	22.8	26.3	0.15
TIMI flow post percutaneous coronary intervention	TIMI 0/1 flow (%)	2.3	2.9	0.53
	TIMI 2 flow (%)	8.9	10.6	0.35
	TIMI 3 flow (%)	88.8	86.5	0.25
Myocardial blush grade 2/3 after percutaneous coronary intervention (%)		78.1	75.8	0.37
TIMI: thrombolysis in myocardial infarction				

Table 3. Three-year clinical outcomes stratified by presence of bifurcation target lesion.

| Variable	≥1 bifurcation target lesion (n=333)	No bifurcation target lesion (n=2,973)	*p*-value	Unadjusted hazard ratio [95% CI]	Adjusted hazard ratio, Cox model [95% CI]
Net adverse clinical events (%)	26.3	27.1	0.77	0.97 [0.77-1.21]	0.99 [0.70, 1.39]
Major adverse cardiac events (%)	22.4	22.2	0.92	1.01 [0.80-1.29]	0.88 [0.60, 1.29]
Death (%)	6.1	6.7	0.72	0.92 [0.58-1.46]	0.74 [0.32, 1.70]
Cardiac death (%)	3.7	3.9	0.84	0.94 [0.52-1.71]	1.17 [0.46, 2.97]
Reinfarction (%)	8.6	7.2	0.41	1.19 [0.79-1.77]	1.05 [0.55, 2.00]
Ischaemic target vessel revascularisation (%)	14.3	14.0	0.86	1.03 [0.76-1.40]	0.86 [0.53, 1.39]
Stent thrombosis (definite or probable) (%)	4.2	5.2	0.42	0.79 [0.45-1.40]	0.54 [0.21, 1.43]
Acute (≤24 hr) (%)	0.9	0.9	0.94	1.05 [0.32-3.48]	0.90 [0.24, 3.37]
Subacute (1 day to 30 days) (%)	0.6	1.7	0.15	0.37 [0.09-1.51]	0.40 [0.07, 2.24]
Late (>30 days to 1 yr) (%)	1.0	1.1	0.88	0.91 [0.28-2.98]	0.76 [0.09, 6.40]
Very late (>1 yr to 3 yr) (%)	1.7	1.8	0.88	0.93 [0.37-2.34]	0.44 [0.05, 3.60]
Major bleeding (non-coronary artery bypass graft related) (%)	7.3	9.1	0.29	0.80 [0.53-1.21]	1.20 [0.66, 2.16]
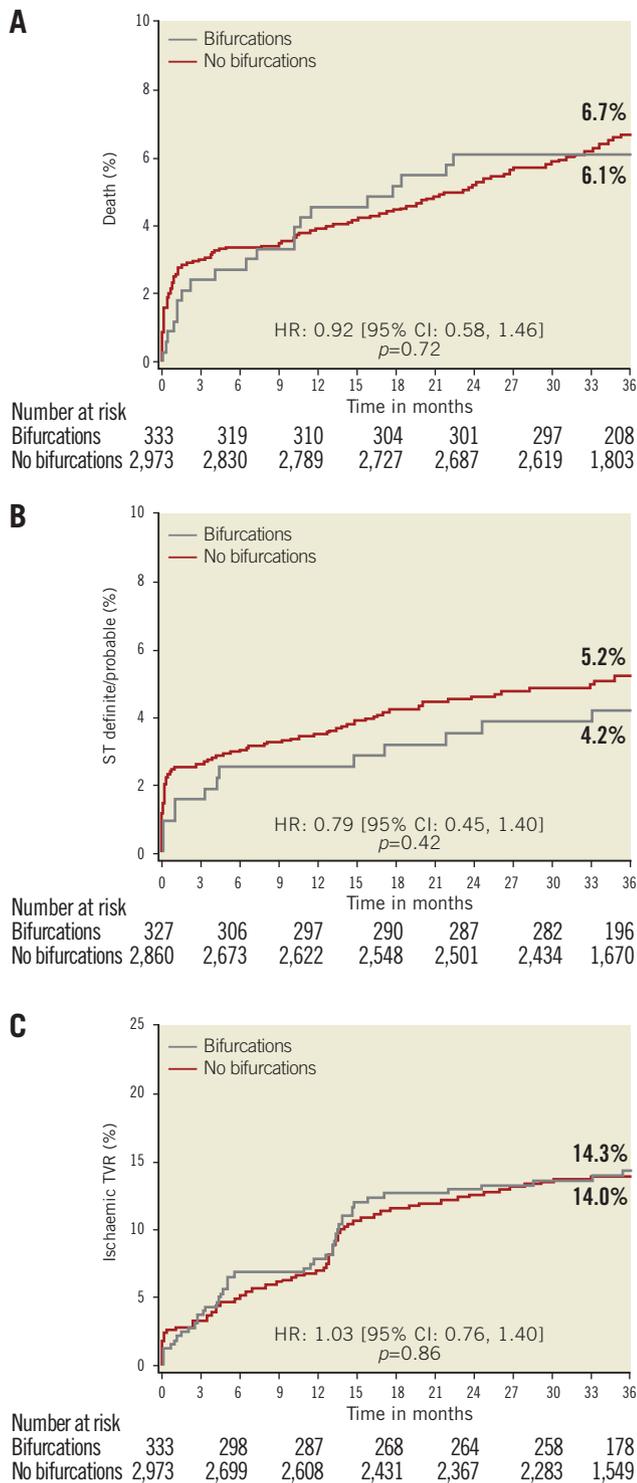
Figure 1. *Three-year Kaplan-Meier event-free survival curves for A) death; B) definite/probable stent thrombosis; and C) ischaemic target vessel revascularisation (stratified by bifurcation target lesion presence). ST: stent thrombosis; TVR: target vessel revascularisation*

sex, and infarct-related artery. A provisional T-stenting technique was used in 93% of patients. Angiographic success rates (residual stenosis ≤30% and TIMI 3 flow in main branch) were similar in BTL and non-BTL patients (97% vs. 99%, p=0.18). There was no difference in acute complications at <24 hours.

The observed frequency of BTL in our study (10%) was somewhat lower than reported in the previous trials of primary PCI[11,12] and planned PCI[13,14]. This difference may in part be related to the protocol-required exclusion of patients who, in the opinion of the investigators, required the implantation of two stents for treatment of BTL. Also, the definition of BTL may vary across the studies (core laboratory vs. investigator assessment). In line with a previous report[11], the main difference between patients with and without BTL from the present study was the more frequent involvement of the left anterior descending artery in patients treated with primary PCI within BTL. This difference in infarct location may be the main reason for the lower ejection fraction observed in such patients. Importantly, STEMI related to the left anterior descending artery[15] is often responsible, together with other concomitant factors like diabetes mellitus[16] and multivessel artery disease presence[17,18], for worse outcomes. The frequency of final TIMI 3 flow and complete ST-segment resolution after PCI were similar in both groups. The rates of TIMI 3 flow were lower than reported in the previous studies (with or without BTL), as the present trial used independent core laboratory evaluation rather than investigator assessment.

Similarly to Frangos et al[12], we found no differences in mortality and major adverse events rates at 30 days between patients with vs. without BTL. Also, the overall three-year mortality did not differ between groups. The impact of BTL on long-term outcomes is probably small compared to that of other factors (i.e., infarct size, time to reperfusion). The presence of BTL was identified as an independent predictor of stent thrombosis in patients undergoing primary PCI with drug-eluting stent implantation in other series[19,20]; however, this was not confirmed by the results of our study (in STEMI) as the rates of acute, subacute, late, and very late stent thrombosis were similar in patients with and without BTL. Surprisingly, in contrast to studies assessing the impact of BTL in patients with stable angina, there was no significant difference in ischaemic target vessel revascularisation rates between groups, although a weak trend was present towards a higher rate of revascularisation when more than one stent was implanted. However, there was no impact of stenting technique (1 vs. >1 stent implanted) on other clinical outcomes. The risk of ischaemic target vessel revascularisation in patients after STEMI is frequently lower than in patients without infarction, as the infarcted territory may be clinically silent when restenosis occurs. Also, up to 70% of patients in the present study were treated with drug-eluting stents, which are known to reduce the risk of target vessel revascularisation when used for BTL treatment[3].

The primary PCI procedure (time from first to last contrast injection) was approximately 10 minutes longer in patients with compared to without BTL, even though door-to-balloon time was similar, suggesting that BTL requires additional interventions after restoration of flow, such as kissing balloon inflation or rewiring of the side branch. Fluoroscopy time was also longer[12] due to more complex techniques being required. Despite a higher contrast load in BTL patients, no difference in the risk of contrast-induced nephropathy was observed between the groups.

Limitations

The main limitation of the study is its non-randomised design, as the study is a subanalysis from a large, multicentre trial. In HORIZONS-AMI, bifurcation lesions in which a provisional approach was planned were enrolled, but the technique of bifurcation treatment was not standardised. This was left to the discretion of the operator, and we were unable to assess the impact of BTL treatment strategy on clinical outcomes properly. However, since a two-stent strategy was reserved by protocol for suboptimal results, a bias toward worse outcomes in the two-stent group would have been expected, which was not seen.

Conclusions

In this large-scale multicentre trial of patents with STEMI, primary PCI in BTL was performed in 10% of cases. Although the PCI procedure of BTL was more complex, the acute results and late outcomes in patients with BTL were comparable to those without BTL.

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Conflict of interest statement

D. Dudek has grant support from Boston Scientific Corporation, St. Jude Medical and Volcano Corporation. He is also a consultant with Boston Scientific Corporation and St. Jude Medical. R. Mehran has received research grants (institutional) from The Medicines Company, BMS/Sanofi and Lilly/Daiichi Sankyo. She is also a consultant for Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, Janssen Pharmaceuticals, Regado Biosciences, Maya Medical, Merck & Co. and The Medicines Company. G.W. Stone is a consultant with Boston Scientific Corporation. The other authors have no conflicts of interest to declare.

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