CLINICAL RESEARCH

Predictors of suboptimal TIMI flow after primary angioplasty for acute myocardial infarction: results from the HORIZONS-AMI trial

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KEYWORDS

- myocardial infarction
- stents
- TIMI flow

Abstract

Aims: The predictors of TIMI flow <3 after PCI in patients with acute myocardial infarction have not been examined in a contemporary, large-scale multicentre prospective study.

Methods and results: The HORIZONS-AMI trial randomised 3,602 patients with STEMI undergoing primary PCI to bivalirudin (n=1,800) vs. unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (n=1,802). A total of 3,845 treated lesions (3,362 vessels) were analysed by the core lab; 2,942 vessels (87.5%) and 2,758 patients (87.1%) had final TIMI 3 flow, while 407 (12.9%) had TIMI flow <3. The independent predictors of TIMI flow <3 were age (OR 1.23 per 10-year increase; 95% CI: 1.12 to 1.35; p<0.0001), anterior MI (OR 1.65; 95% CI: 1.33 to 2.05; p<0.0001), baseline TIMI flow grade 0/1 (OR 2.79; 95% CI: 2.14 to 3.62; p<0.0001), and lesion length (OR 1.05 per 10 mm increase; 95% CI: 1.02 to 1.09; p=0.005). The three-year mortality of patients in whom final TIMI 3 flow was achieved was significantly lower than that of patients in whom TIMI 3 flow was not achieved (5.5% vs. 10.5%; p<0.0001).

Conclusions: In this large-scale, randomised trial, failure to restore normal TIMI flow after primary PCI in STEMI occurred in 12.9% of patients, and was associated with patient-related factors (age), anatomical factors (anterior MI location), and angiographic factors (baseline TIMI 0/1 flow and lesion length). Failure to achieve TIMI 3 flow continues to be a powerful predictor of mortality after primary PCI in the contemporary era. Clinical Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT00433966.

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Introduction

Primary percutaneous coronary intervention (PCI) improves survival rates in patients with acute myocardial infarction (MI) as compared with thrombolytic therapy, in large part due to better and sustained antegrade epicardial perfusion (thrombolysis in myocardial infarction [TIMI] grade 3 flow)[1]. As compared with balloon angioplasty, primary PCI with stent implantation results in a significant and persistent reduction in recurrent ischaemia and target vessel revascularisation[2,3]. Hence, current guidelines recommend primary PCI with stent implantation as the treatment of choice for patients with evolving ST-segment elevation myocardial infarction (STEMI)[4]. Nevertheless, failure to achieve TIMI 3 flow (i.e., suboptimal TIMI flow) after primary PCI still occurs in up to 5-23%[2,3,5,6] of patients. Prior studies have reported a strong relationship between suboptimal final TIMI flow and mortality[5,7,8]. However, the impact of suboptimal TIMI flow on long-term follow-up (>1 year) has never previously been reported. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI)[9] trial provides a unique opportunity to investigate the long-term prognostic utility and baseline clinical and angiographic predictors of suboptimal TIMI flow after primary PCI in the contemporary era.

Methods

PATIENT POPULATION AND STUDY PROTOCOL

The HORIZONS-AMI trial design has been described elsewhere in detail[10]. In brief, HORIZONS-AMI was a prospective, randomised, multicentre trial of 3,602 STEMI patients undergoing primary PCI. Patients were randomised prior to angiography in a 1:1 ratio to either unfractionated heparin (UFH) plus routine use of a glycoprotein IIb/IIIa inhibitor (GPI) or bivalirudin monotherapy. Following angiography, 3,006 eligible patients underwent a second randomisation (3:1) to either TAXUS™ Express2™ paclitaxel-eluting stents (PES) (Boston Scientific, Natick, MA, USA) or uncoated Express2™ bare metal stents (BMS) (Boston Scientific). The decision whether to use a manual thrombus aspiration device before or during PCI was left to the operator's discretion. A clopidogrel loading dose (either 300 mg or 600 mg) was administered prior to catheterisation, followed by 75 mg PO daily for at least six months (one year recommended).

STUDY OBJECTIVES AND DEFINITIONS

The primary objective of this study was to evaluate the angiographic, clinical and procedural predictors of core-laboratory assessed suboptimal final TIMI flow (<3) after stent implantation. A secondary objective was to assess the impact of final suboptimal TIMI flow (TIMI 0-2 vs. TIMI 3) on three-year clinical outcomes. All adverse events were adjudicated by an independent clinical events committee, blinded to pharmacology and stent assignment, after review of original source documentation.

ANGIOGRAPHIC ANALYSIS

An independent angiographic laboratory performed quantitative coronary angiography on all baseline and post-PCI lesions (CMS; Medis Medical Imaging Systems, Leiden, The Netherlands), blinded to randomisation assignment and clinical outcomes (Cardiovascular Research Foundation, New York, NY, USA). TIMI flow in the infarct vessel was assessed as previously reported[11].

STATISTICAL ANALYSIS

Categorical variables were compared by chi-square analysis or Fisher's exact test. Continuous variables are presented as mean ± SD, median and interquartile ranges (IQR) and were compared by Student's t-test or Wilcoxon rank-sum test, as appropriate. Kaplan-Meier methods were used to derive the event rates at follow-up and to plot time-to-event curves; comparisons were made using the log-rank test. The Cox proportional hazards model was used to derive the independent predictors of death and cardiac death, and stepwise logistic regression was used to determine the independent predictors of final suboptimal TIMI flow (<3). Lesion level variables were summarised as worst TIMI flow per patient if multiple lesions were present. The p-value to enter and exit each model was 0.2/0.1. All statistical tests were two-tailed. Statistical significance was set at a level of 0.05. All analyses were performed with SAS 9.0 (Cary, NC, USA).

Results

FREQUENCY AND CORRELATES OF SUBOPTIMAL FINAL TIMI FLOW

PCI was performed in 3,345 patients (92.9%), among whom stents were implanted in 3,226 (96.4%). A total of 3,845 stented lesions (3,362 vessels in 3,165 patients) were analysed by the core lab and comprise the current study cohort; 2,758 patients (87.1%) had final TIMI 3 flow, and 407 (12.9%) had TIMI flow <3. Compared to patients with final TIMI 3 flow, patients with final TIMI flow <3 were more likely to be older, have more renal insufficiency, more evidence of heart failure (Killip class 2-4) and left ventricular dysfunction at presentation, and were less likely to be smokers or to have prior MI or PCI. Additionally, patients with final TIMI flow <3 had significantly longer times from symptom onset to first hospital arrival, from symptom onset to balloon, and from door to balloon **(Table 1)**.

Lesions in patients with final TIMI flow <3 were more likely to be located in the proximal and mid left anterior descending artery, had a larger baseline thrombus burden, were more complex (by ACC/AHA classification), and had lower epicardial TIMI flow before the procedure **(Table 2)**. An aspiration catheter was used more frequently in patients with final TIMI flow <3 compared with those with TIMI 3 flow (14.8% vs. 10.9%; p=0.02). TIMI 3 flow was restored in a comparable percentage of patients randomised to bivalirudin and UFH plus GPI (86.6% vs. 88.3%, respectively, p=0.15).

PREDICTORS OF SUBOPTIMAL TIMI FLOW

By multivariable analysis, the independent predictors of TIMI flow <3 were age (OR 1.23 per 10-year increase; 95% CI: 1.12 to 1.35; p<0.0001), anterior MI (OR 1.65; 95% CI: 1.33 to 2.05; p<0.0001), baseline TIMI flow grade 0/1 (OR 2.79; 95% CI: 2.14 to 3.62; p<0.0001), and lesion length (OR 1.05 per 10 mm increase; 95% CI: 1.02 to 1.09; p=0.005).

Table 1. Baseline characteristics in patients with final TIMI <3 flow vs. TIMI 3 flow.

		Final TIMI <3 (n=407)	Final TIMI 3 (n=2,758)	*p*-value
Age, median [IQR]		62.4 [55.3, 72.3]	59.3 [51.9, 69.0]	<0.0001
Male, % (n)		76.4% (311/407)	77.4% (2,134/2,758)	0.66
Body mass index, median [IQR], kg/m²		27.4 [24.8, 30.5]	27.1 [24.5, 30.1]	0.22
Hypertension, % (n)		55.0% (224/407)	51.5% (1,420/2,756)	0.18
Hyperlipidaemia, % (n)		38.1% (155/407)	43.2% (1,191/2,756)	0.05
Current smoking, % (n)		35.3% (143/405)	49.1% (1,348/2,747)	<0.0001
Diabetes mellitus, % (n)		16.7% (68/407)	16.1% (444/2,756)	0.76
Insulin-treated		5.7% (23/407)	4.2% (117/2,756)	0.20
Prior MI, % (n)		7.1% (29/407)	10.7% (296/2,756)	0.02
Prior PCI, % (n)		5.4% (22/407)	10.7% (294/2,755)	0.0009
Prior CABG, % (n)		2.5% (10/407)	2.5% (68/2,756)	0.99
Prior angina, % (n)		21.1% (86/407)	22.0% (606/2,755)	0.69
Peripheral vascular disease, % (n)		3.0% (12/406)	4.6% (127/2,756)	0.13
Renal insufficiency*, % (n)		4.7% (19/406)	2.5% (70/2,756)	0.01
History of CHF, % (n)		1.2% (5/407)	2.8% (78/2,756)	0.06
Killip class, % (n)	Class 1	88.5% (360/407)	91.9% (2,531/2,753)	0.02
	Class 2	8.4% (34/407)	6.9% (190/2,753)	0.29
	Class 3	1.2% (5/407)	0.7% (18/2,753)	0.20
	Class 4	2.0% (8/407)	0.5% (14/2,753)	0.004
LVEF, median [IQR], %		55.1 [45.9, 64.1]	60.2 [51.3, 68.1]	<0.0001
Study timing PCI	Symptom onset to first hospital¶, median [IQR], min	130 [77.0, 260.0]	110 [61.0, 195.0]	<0.0001
	Door-to-balloon‡, median [IQR], min	100 [80.0, 140.0]	97 [71.0, 133.0]	0.03
	Symptom onset to balloon, median [IQR], min	268.0 [181.0, 393.0]	215.0 [157.0, 327.0]	<0.0001
Discharge medications	B-blockers	90.3% (363/402)	91.2% (2,509/2,752)	0.57
	ACE inhibitor or ARB	86.0% (333/387)	82.7% (2,245/2,716)	0.1
	Statin	95.3% (369/387)	96.0% (2,608/2,716)	0.53
	Aspirin	97.7% (378/387)	99.0% (2,689/2,716)	0.04
	Thienopyridine	99.5% (385/387)	99.6% (2,704/2,716)	0.69

*Renal insufficiency was defined as a calculated creatinine clearance rate of <60 mL/min as determined by the Cockcroft-Gault equation. ¶Symptom onset to outside hospital or study hospital emergency department. ‡Door-to-balloon is calculated as arrival at outside hospital or study hospital emergency department to first balloon inflation. ACE: angiotensin-converting enzyme; ARB: adrenergic receptor antagonists; CABG: coronary artery bypass grafting; IQR: interquartile range; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

IMPACT OF FINAL TIMI FLOW ON CLINICAL OUTCOMES

The 30-day and three-year rates of major adverse cardiovascular events (MACE) and bleeding were significantly higher in patients with TIMI flow <3 compared to those with TIMI 3 flow (**Table 3** and **Figure 1**). After multivariable adjustment for differences in baseline covariates, final TIMI flow <3 independently predicted all-cause death and cardiac death at three years (**Table 4**). STEMI patients with final TIMI flow <3 compared with those with TIMI 3 flow had an adjusted HR for all-cause mortality of 2.26 (95% CI: 1.49 to 3.44; p=0.0001) and an adjusted HR for cardiac mortality of 3.04 (95% CI: 1.90 to 3.44; p=0.0001) at three years. Other independent predictors of three-year cardiac mortality in addition to TIMI flow <3 were a history of diabetes, Killip class 2-4, creatinine clearance <60 ml/min and treatment in the left anterior descending artery.

Discussion

The present analysis from the large-scale, multicentre, prospective randomised HORIZONS-AMI trial demonstrates that failure to achieve normal TIMI flow after primary PCI in STEMI is relatively common (12.9%), and is associated with patient-related factors (age), anatomical factors (anterior MI location) and angiographic factors (baseline TIMI 0/1 flow and lesion length). In addition, not achieving TIMI 3 flow continues to be a powerful predictor of short and long-term mortality in the contemporary primary PCI era.

SUBOPTIMAL TIMI FLOW AND IMPACT ON MORTALITY

The findings of the present study are in agreement with previous reports showing the relationship between final suboptimal epicardial TIMI flow after PCI and mortality in STEMI patients[5,7,8,12,13]. In a pooled analysis from the four major Primary Angioplasty in

Table 2. Procedure-related factors and core angiographic laboratory characteristics in lesions with final TIMI <3 flow vs. TIMI 3 flow.

		Final TIMI <3 (n=522 lesions)	Final TIMI 3 (n=3,323 lesions)	*p*-value
Baseline target lesion measures, median [IQR]				
Lesion target vessel, % (n)	Left anterior descending artery	48.9% (255/522)	38.8% (1,290/3,323)	<0.0001
	Right coronary artery	36.4% (190/522)	45.0% (1,494/3,323)	0.0002
	Left circumflex coronary artery	13.2% (69/522)	15.3% (510/3,323)	0.21
	Saphenous vein graft	1.5% (8/522)	0.9% (29/3,323)	0.15
Lesion length, median [IQR], mm		15.0 [10.0, 21.1]	14.6 [10.4, 20.1]	0.97
Lesion length <10 mm		28.5% (144/506)	23.1% (755/3,272)	0.008
Lesion length 10-20 mm		44.7% (226/506)	51.9% (1,697/3,272)	0.002
Lesion length >20 mm		26.9% (136/506)	25.1% (820/3,272)	0.38
Reference vessel diameter, median [IQR], mm		2.9 [2.5, 3.3]	2.9 [2.5, 3.2]	0.11
Minimal luminal diameter, median [IQR], mm		0.0 [0.0, 0.5]	0.2 [0.0, 0.7]	<0.0001
Diameter stenosis, median [IQR], %		100.0 [80.5, 100.0]	93.3 [75.7, 100.0]	<0.0001
Thrombus, % (n)		79.1% (413/522)	69.0% (2,291/3,319)	<0.0001
Thrombus area, mean±SD, mm^3		36.96±32.25 (372)	32.11±22.48 (2,183)	0.02
ACC/AHA lesion class, % (n)	A	3.1% (16/522)	3.7% (123/3,323)	0.47
	B1	7.3% (38/522)	11.4% (379/3,323)	0.005
	B2	7.7% (40/522)	13.2% (438/3,323)	0.0004
	C	82.0% (428/522)	71.7% (2,383/3,323)	<0.0001
	>B1	89.7% (468/522)	84.9% (2,821/3,323)	0.004
TIMI flow grade, % (n)	0/1	78.4% (331/422)	57.3% (1,684/2,940)	<0.0001
	2	14.9% (63/422)	13.6% (401/2,940)	0.47
	3	6.6% (28/422)	29.1% (855/2,940)	<0.0001
Final target lesion measures, median [IQR]				
Reference vessel diameter, mm		2.9 [2.5, 3.4]	2.9 [2.6, 3.3]	0.30
Minimal luminal diameter, mm		2.3 [1.9, 2.7]	2.4 [2.0, 2.7]	0.001
Diameter stenosis, %		19.9 [13.7, 28.7]	18.2 [12.3, 24.8]	<0.0001
Thrombus		7.2% (35/484)	1.7% (57/3,360)	<0.0001
Distal embolisation		11.2% (54/484)	1.6% (54/3,357)	<0.0001
Procedure-related factors, median [IQR]				
No. of stents, mean±SD, n		1.6±1.0	1.5±0.8	0.01
Total stent length, mm		24.0 [20.0, 41.0]	24.0 [20.0, 36.0]	0.01
Predilatation balloon used		84.3% (339/402)	77.5% (2,112/2,725)	0.002
Post-stent dilatation balloon used		44.7% (163/365)	37.7% (966/2,562)	0.01
Number of lesions treated		1.1±0.4	1.1±0.4	0.36
Direct stenting		22.7% (83/365)	31.8% (867/2,723)	0.0004
Aspiration catheter		14.8% (59/399)	10.9% (299/2,745)	0.02
Thrombectomy device		3.0% (12/401)	0.7% (20/2,730)	0.0003
Reason for aspiration catheter usage	Bail-out	100% (2/2)	52.9% (9/17)	0.48
	Routine/planned	0.0% (0/2)	47.1% (8/17)	0.48
Distal protection device		0.5% (2/402)	0.6% (17/2,746)	1.00
Randomisation to bivalirudin		13.4%	86.6%	0.15
Randomisation to UFH plus GPI		11.7%	88.3%	

ACC: American College of Cardiology; AHA: American Heart Association; IQR: interquartile range; UFH: unfractionated heparin

Myocardial Infarction (PAMI) trials[7], patients with post-procedure TIMI flow <3 (7.5%) had a fourfold increased risk of six-month mortality. Likewise, patients with suboptimal TIMI flow (5%) after stent implantation experienced a significant threefold increased risk of

death at six months in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial[8]. Finally, in the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) trial[5] patients with TIMI flow <3 (15%) had

Table 3. 30-day and 3-year clinical outcomes according to final TIMI flow.

	Final TIMI <3 (n=407)	Final TIMI 3 (n=2,758)	Relative risk [95% CI]	*p*-value
30-day				
MACE	9.6% (39)	4.0% (109)	2.47 [1.72,3.57]	<0.0001
Death	5.9% (24)	1.5% (42)	3.93 [2.38,6.49]	<0.0001
Cardiac	5.4% (22)	1.5% (40)	3.78 [2.25,6.36]	<0.0001
Non-cardiac	0.5% (2)	0.1% (2)	6.98 [0.98,49.54]	0.02
Reinfarction	2.5% (10)	1.7% (47)	1.46 [0.74,2.89]	0.27
Q-wave	1.7% (7)	1.4% (37)	1.30 [0.58,2.91]	0.53
Non-Q-wave	0.8% (3)	0.4% (10)	2.08 [0.57,7.55]	0.26
Death or reinfarction	7.9% (32)	3.0% (82)	2.69 [1.79,4.04]	<0.0001
Stroke	0.8% (3)	0.4% (11)	1.88 [0.52,6.72]	0.33
Target vessel revascularisation	3.5% (14)	2.1% (57)	1.69 [0.94,3.03]	0.07
Definite or probable stent thrombosis	4.5% (18)	2.0% (54)	2.30 [1.35,3.92]	0.002
Major bleeding (non-CABG related)	12.7% (51)	6.3% (173)	2.05 [1.50,2.80]	<0.0001
3-year				
MACE	24.0% (96)	21.1% (567)	1.21 [0.97,1.50]	0.08
Death	10.5% (42)	5.5% (148)	2.01 [1.43,2.83]	<0.0001
Cardiac	7.5% (30)	2.9% (78)	2.69 [1.77,4.10]	<0.0001
Non-cardiac	3.2% (12)	2.7% (70)	1.23 [0.67,2.27]	0.51
Reinfarction	7.2% (27)	7.2% (189)	1.02 [0.68,1.53]	0.92
Q-wave	3.4% (13)	3.6% (96)	0.96 [0.54,1.71]	0.88
Non-Q-wave	3.8% (14)	4.0% (103)	0.98 [0.56,1.71]	0.94
Death or reinfarction	16.5% (66)	11.7% (315)	1.49 [1.15,1.95]	0.003
Stroke	1.6% (6)	1.4% (38)	1.12 [0.47,2.64]	0.80
Target vessel revascularisation	12.7% (48)	14.7% (385)	0.89 [0.66,1.20]	0.45
Definite or probable stent thrombosis	6.6% (26)	4.8% (127)	1.45 [0.95,2.21]	0.08
Major bleeding (non-CABG related)	13.6% (54)	7.9% (214)	1.78 [1.32,2.40]	0.0001
MACE (death, MI, ischaemic TVR or stroke). Stent thromboses were classified by Academic Research Consortium criteria.				
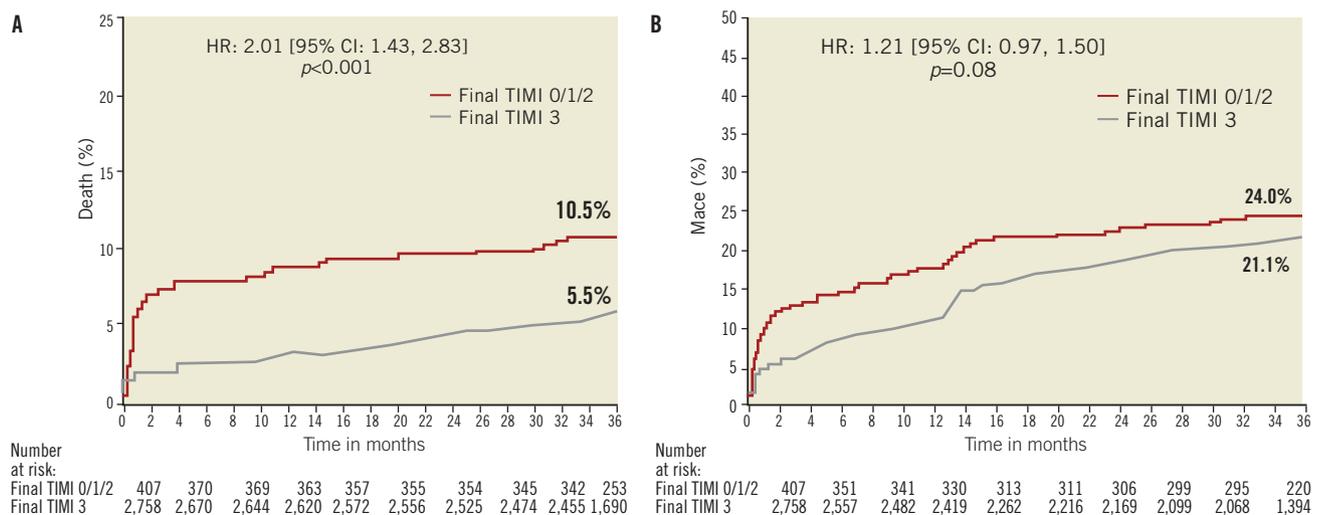
Figure 1. *Time-to-events curves for patients with final suboptimal TIMI flow (TIMI 0-2) vs. TIMI 3 flow. Three-year cumulative event curves for (A) all-cause mortality, and (B) MACE.*

threefold higher mortality at six months. The present study extends these findings by demonstrating the prognostic value of final TIMI flow <3 in a larger population with fewer exclusion criteria than from earlier studies, treated with contemporary pharmacotherapy. While the PAMI trials[7] and APEX-AMI[5] included patients within six hours of symptom onset, and the CADILLAC trial[8] selected patients with

Table 4. Independent predictors of death, cardiac death and TIMI flow <3 post stenting by multivariable analyses.

Predictors	HR [95% CI]	p-value
All-cause death*		
Final TIMI 0/1/2 (vs. TIMI 3)	2.26 [1.49, 3.44]	0.0001
History of CHF	2.47 [1.31, 4.63]	0.005
History of peripheral vascular disease	2.03 [1.17, 3.55]	0.01
Age (per 10-year increase)	1.41 [1.16, 1.71]	0.0005
Killip class 2-4	2.49 [1.65, 3.77]	<0.0001
Insulin-dependent DM	1.54 [0.86, 2.75]	0.15
Creatinine clearance <60	2.00 [1.29, 3.11]	0.002
Number of stents implanted (per 1-stent increase)	1.17 [0.99, 1.38]	0.07
LAD treated	1.98 [1.21, 3.26]	0.007
History of MI	2.21 [1.46, 3.34]	0.0002
Cardiac death*		
Final TIMI 0/1/2 (vs. TIMI 3)	3.04 [1.90, 4.87]	<0.0001
History of diabetes mellitus	2.43 [1.55, 3.82]	0.0001
Killip class 2-4	2.86 [1.75, 4.68]	<0.0001
Creatinine clearance <60	3.26 [2.10, 5.06]	<0.0001
LAD treated	3.41 [1.64, 7.12]	0.001
Predictors	**OR [95% CI]**	**p-value**
Final TIMI flow <3¶		
Age (per 10-year increase)	1.23 [1.12, 1.35]	<0.0001
Anterior MI	1.65 [1.33, 2.05]	<0.0001
Baseline TIMI 0/1	2.79 [2.14, 3.62]	<0.0001
Lesion length (per 10 mm increase)	1.05 [1.02, 1.09]	0.005

*The covariates considered in the model are: age, sex, race, U.S. treatment, body mass index, Killip class 2-4, anaemia, platelet count, creatinine clearance, randomisation to bivalirudin (vs. UFH plus GPI), randomisation to TAXUS PES (vs. BMS), hypertension, hyperlipidaemia, smoking, diabetes, insulin-dependent diabetes, prior MI, prior CABG, history of angina, congestive heart failure, peripheral vascular disease, clopidogrel loading dose, pre-randomisation heparin, number of stents, baseline TIMI 0/1, final TIMI flow, and LAD location.
¶The covariates considered in the model are: randomised to bivalirudin, DES randomisation, age, gender, race, BMI, pre-randomisation heparin, hypertension, hyperlipidaemia, smoking, diabetes, insulin-dependent diabetes, anaemia, prior MI, prior PCI, prior CABG, prior CAD, angina, congestive heart failure, Killip class 2-4, peripheral vascular disease, time from symptom onset to first hospital, platelets, chronic renal insufficiency, AMI, LVEF, LAD location, number of stents, reference vessel diameter, any thrombus, any ulceration, any aneurysm, any bifurcation, calcification moderate/severe, multilesion treatment, multivessel treatment, lesion length, baseline TIMI 0/1.

angiographically less complex anatomy, HORIZONS-AMI enrolment criteria permitted a broader clinical presentation (within 12 hours of symptom onset) and more complex coronary anatomy and angiographic lesion subsets. Moreover, the present analysis represents the longest follow-up (three years) thus far describing the impact of epicardial TIMI flow grade at the index PCI on very late mortality. Of note, suboptimal post-PCI TIMI flow was an independent predictor of mortality even after correction for baseline TIMI flow; and a three-year higher cumulative rate of mortality in patients with suboptimal TIMI flow was driven by events within the initial two months. The survival benefit of PCI over thrombolytic therapy is in large part due to the achievement of higher rates of epicardial TIMI 3 blood flow[1]. The pathophysiology of slow flow and no-reflow after primary PCI is multifactorial[14]. Despite TIMI flow grade interpretation

being subject to interobserver variability[15], it is a simple, quick and reliable evaluation that strongly predicts long-term mortality (although other surrogate markers of impaired myocardial perfusion have higher sensitivity than TIMI flow grade for the prediction of death, including myocardial blush grade, ST-segment resolution and TIMI frame count)[5,16,17].

MODIFIABLE PREDICTORS OF FINAL TIMI FLOW
In our study, baseline TIMI 0/1 flow was a powerful predictor of suboptimal final TIMI 3 flow. Similarly, in the APEX-AMI trial[5] primary PCI study, the independent predictors of achieving suboptimal TIMI flow after PCI were age, time to treatment and pre-PCI TIMI flow grade 0/1. Ndrepepa et al[13] reported that abnormal baseline TIMI flow is an independent predictor of no-reflow after PCI. Stone et al[7] found preprocedural TIMI <3 flow was an independent predictor of mortality in patients with STEMI. Nevertheless, the lack of success of facilitated PCI[18-20] in improving final coronary flow with half dose[6] and full dose[21] thrombolytic agents or improving prognosis after STEMI highlights the inherent differences between the spontaneous and pharmacologic-induced restoration of epicardial perfusion prior to PCI. Conversely, use of adjunctive manual thrombectomy in STEMI patients has been associated with significant improvement in coronary flow before stent implantation as well as postprocedural epicardial and myocardial perfusion with less distal embolisation, and possible benefits in long-term survival[22]. While a large-scale randomised trial is ongoing to determine the ability of aspiration thrombectomy to reduce mortality in STEMI (Thrombus Aspiration in Myocardial Infarction [TASTE], NCT01093404), the present data from the HORIZONS-AMI trial support this hypothesis. The HORIZONS-AMI trial was designed before the routine incorporation of manual thrombus aspiration in the setting of STEMI and this technique was used in only 10% of the patients. Furthermore, the higher usage of thrombus aspiration catheters or any thrombectomy device in patients with suboptimal TIMI flow was driven by unplanned indication (e.g., bailout or to treat suboptimal results). Thus, the impact of these devices in mitigating suboptimal final TIMI flow in the present analysis could not be properly assessed. Finally, there is also an ongoing debate regarding the use of superselective intracoronary administration of abciximab in STEMI patients. Intracoronary infusion of abciximab significantly reduced thrombus volume with improvement in final TIMI flow[23], as well as resulting in a significant reduction in infarct size in the recent Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction (INFUSE-AMI) trial[24]. Larger studies will be needed to determine whether the degree of reduction in infarct size and improvement in TIMI flow obtained with the intracoronary infusion of abciximab translates into improved clinical outcomes.

In the present analysis, there was no interaction between time to treatment (symptom onset to balloon dilatation) and either suboptimal final TIMI flow or mortality. Although the mortality benefit of thrombolytic therapy for acute MI is strongly dependent on time to treatment[1], its role in patients undergoing primary PCI remains controversial;

some studies suggest that time delay to treatment increases mortality[5], whereas others report no effect[25]. The lack of correlation between time to treatment and suboptimal TIMI flow and mortality in the present analysis suggests that the survival benefit from primary PCI may be influenced by factors other than myocardial salvage (e.g., major bleeding, transfusion, and thrombocytopenia). Although the exact mechanism is unclear, it is possible that an association between time to treatment and suboptimal TIMI flow has been overridden by other powerful covariates such as baseline TIMI flow. However, the finding that anterior MI was an independent correlate of suboptimal final TIMI flow corroborates previous studies that have demonstrated a close correlation between infarct size, MI involving the LAD distribution, and the presence of abnormal TIMI flow[13,26]. LAD infarctions have a higher initial area at risk[13,27], cause more severe systolic dysfunction prior to PCI, and are more likely to result in distal embolisation after PCI, a potential mechanism of slow flow and no-reflow.

Limitations

The present data represent the largest QCA database pertaining to STEMI patients; nevertheless, we cannot completely rule out the possibility that not all multivariable correlates of suboptimal TIMI flow were identified. Finally, we did not assess the association between final TIMI flow and other angiographic surrogate markers of myocardial perfusion (e.g., myocardial blush and TIMI frame count); we therefore could not investigate their relative risk prediction of clinical outcomes.

Conclusions

In the large-scale, multicentre, prospective, randomised HORIZONS-AMI trial, absence of normal TIMI 3 flow after primary PCI in STEMI occurred in 12.9% of patients, and was associated with patient-related factors (age), anatomical factors (anterior MI location), and angiographic factors (baseline TIMI 0/1 flow and lesion length). Failure to achieve TIMI 3 flow continues to be a powerful predictor of mortality after primary PCI in the contemporary reperfusion era.

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Conflict of interest statement

R. Mehran received a research grant from Sanofi-Aventis, honoraria from The Medicines Company, Abbott Vascular, Sanofi-Aventis, Bristol-Myers Squibb, Astra-Zeneca and Cordis. She is a consultant or on the advisory board of Eli Lilly and Daiichi Sankyo. B. Witzenbichler received honoraria from Boston Scientific and The Medicines Company. G. Guagliumi received research grants from Medtronic, Boston Scientific, LightLab Imaging and Abbott Vascular and is a consultant and/or on the advisory board of Boston Scientific, Volcano and Cordis. D. Dudek received honoraria from Nycomed. M. Fahy is an employee of the Cardiovascular Research Foundation. B. Brodie received honoraria from The Medicines Company and MedRad/Possis. G. Dangas received honoraria from The Medicines Company, Sanofi-Aventis, Bristol-Myers Squibb, Astra-Zeneca, Cordis and Abbott Vascular. He is a consultant and/or on the advisory board of Eli Lilly and Daiichi Sankyo. G. Stone is a consultant and/or on advisory board of The Medicines Company, Abbott Vascular, Boston Scientific and Medtronic. The other authors have no conflicts of interest to declare.

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