The impact of time-to-balloon on outcomes in patients undergoing modern primary angioplasty for acute myocardial infarction

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ABSTRACT

Introduction: The importance of time-to-primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction has been controversial. We examine the relationship between time-to-treatment and short- to medium-term clinical outcomes.

Methods: In a prospective observational study of data collected from our institution's angioplasty database between June 2001 and May 2003, 208 consecutive patients (mean age 56.0 [range, 28–90] years; 88.5 percent men; 23.6 percent with diabetes mellitus) with ST-segment elevation myocardial infarction (STEMI) and who underwent primary PCI without antecedent fibrinolytic therapy were analysed. With adjustments for appropriate covariates, logistic regressions were performed to assess the relationship between symptom-to-balloon time, door-to-balloon time and the studied outcomes, which were mortality and major adverse cardiac event (MACE) defined as death, myocardial infarction and repeat target vessel revascularisation.

Results: Prolonged symptom-to-balloon time (median time, 3 hours 55 minutes) significantly increased the MACE rate at one month (odds-ratio [OR], 1.45; 95 percent confidence interval [CI], 1.09–1.92; p-value is 0.011) and six months (OR, 1.19; 95 percent CI, 1.01-1.41; p-value is 0.046) but not mortality (at one month, p-value is 0.25; at six months, p-value is 0.87) after adjusting for relevant covariates. However, door-to-balloon time (median time, 110 minutes) did not significantly influence mortality (mortality at one month, p-value is 0.73; six months, p-value is 0.64) and MACE (MACE at one month, p-value is 0.71; six months, p-value is 0.08) at one and six months.

Conclusion: Symptom-to-balloon time is an important predictor of MACE in the short- and medium-term in contrast to door-to-balloon time. Improving public awareness and accessibility of health services to patients with STEMI is essential in reducing poor outcomes.

Keywords: angioplasty, balloon angioplasty, ischaemic heart disease, myocardial infarction, percutaneous coronary intervention

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INTRODUCTION

Rapid time to treatment with fibrinolytic therapy is associated with lower mortality in patients with acute ST-segment elevation myocardial infarction (STEMI).[1-3] However, the importance of time-to-primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) remains controversial. Some reports suggested a delay in door-to-balloon time to be the major outcome predictor but not symptom-to-balloon time.[4] Others found symptom-to-balloon time to be more important.[5, 6] Our study aimed to evaluate, in a single-centre cohort of patients with acute STEMI, the relationship between delay in symptom-to-treatment and door-to-treatment time on short- to medium-term clinical outcomes.

METHODS

Primary PCI has replaced fibrinolytic therapy as the main reperfusion strategy over the last few years and is available as a service throughout 24 hours. Besides managing acute STEMI patients presented to National University Hospital (NUH) emergency department (ED), our catheterisation laboratory also received patients from Tan Tock Seng Hospital (TTSH) and Alexandra

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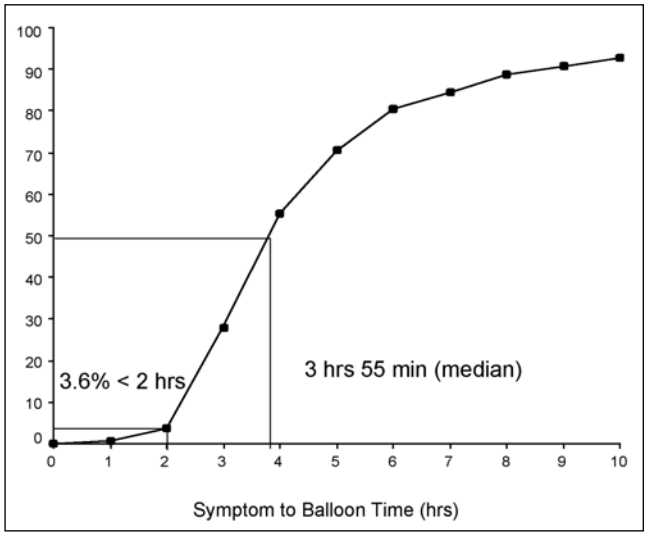

Fig. 1 Cumulative frequency curves of symptom-to-balloon time. The median reperfusion time was 3 hours 55 minutes, and 3.6% of patients achieved reperfusion in < 2 hours.

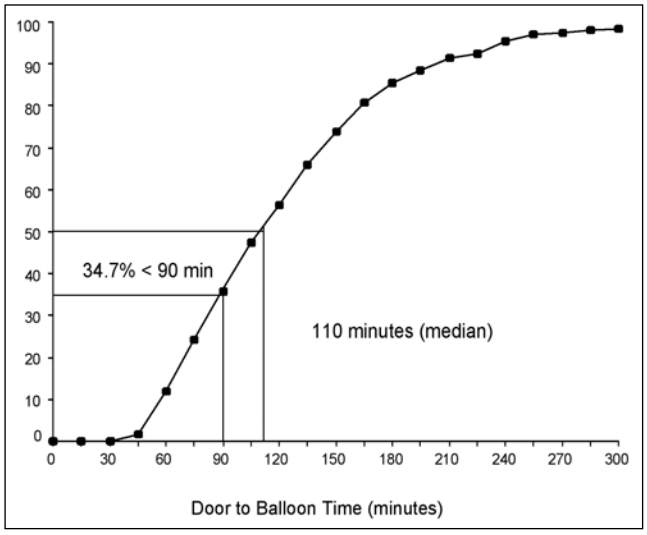

Fig. 2 Cumulative frequency curves of door-to-balloon time. The median door-to-balloon time was 110 minutes, and 34.7% of patients achieved a door-to-balloon time of < 90 minutes.

Hospital (AH), which are located approximately 12.4 km and 2.95 km away, respectively. In this prospective observational study, patients with acute STEMI, defined as a patient with chest pain history accompanied by electrocardiographical (ECG) evidence of ST-segment elevation of at least 0.1 mV (1 mm) in two or more ECG leads, were studied. Between June 2001 and May 2003, a total of 208 consecutive patients with STEMI who underwent primary PCI (without antecedent fibrinolytic therapy) were included.

Symptom-to-balloon time was defined as the interval between the time of patient's reported symptom(s) onset and time of first balloon inflation or device deployment. Door-to-balloon time was the interval between the time of patient registration at ED and time of first balloon inflation or device deployment. Regular office hours at NUH were from 0800 to 1730 hours, Mondays to Fridays, and 0800 to 1230 hours on Saturdays. Any other hours outside regular office hours were defined as after hours, and these include public holidays.

NUH used a comprehensive, computerised patient database system that included Emergency Database System (EMDS) and Computerised Patient Support System (CPSS). EMDS archives all patients' emergency admission records while CPSS is a comprehensive, state-of-the-art electronic medical records system containing case summaries, prescriptions, radiology and laboratory test results. Our catheterisation laboratory has also established its own database (4D Client, 4D Inc., San Jose, CA, USA, 1995–2004) to record all invasive cardiac percutaneous interventions performed since February 2001. All patients' demographics, detailed timeline including time of onset of chest pain, time of arrival at the hospital ("door" time), and time of first balloon inflation (or device deployment) during the primary angioplasty procedure ("balloon time"), were acquired from the above respective databases.

Patients were divided into several pre-specified groups, first by time from symptom onset to first balloon inflation, and then by door time to first balloon inflation. Baseline characteristics, mortality rates and major adverse cardiac event (MACE) rates were examined across these time categories. The primary endpoints of this analysis were mortality rate and MACE rate at one and six months post-event. MACE was defined as death, myocardial infarction and repeat target vessel revascularisation. Further analysis to examine the impact of door-to-balloon time of < 90 minutes versus ≥ 90 minutes within the same symptom-to-balloon time was performed. Nurse coordinators obtained clinical follow-up at one and six months by telephone contact and during any interim inpatient hospitalisations.

All statistical analyses were performed using Statistical Package for Social Sciences for Windows version 11.5 (SPSS Inc, Chicago, IL, USA). Univariate analysis was performed to compare patients' characteristics among the categories of symptom-to-balloon time and door-to-balloon time. Categorical variables were compared using chi-square/Fisher's exact test. Continuous variables were compared using ANOVA/Kruskal-Wallis test as appropriate. Logistic regressions were carried out to assess the relationship between symptom-to-balloon time, door-to-balloon time and the studied outcomes, with adjustments for appropriate covariates. Statistical significance was assumed if $p < 0.05$. Further analysis by comparing door-to-balloon time, in two groupings of < 90

Table I. Baseline variables by symptom-to-balloon time.

Baseline variables	Symptom-to-balloon time				
	< 2 hours (n=7)	2–4 hours (n=100)	4–6 hours (n=48)	> 6 hours (n=39)	p-value
% of total patients	3.6%	51.6%	24.7%	20.1%	N/A
Age ≤ 70 years	7 (100%)	87 (87%)	39 (81.3%)	34 (87.2%)	0.537
Age (years) (mean ± SD)	50.1 ± 8.3	54.3 ± 12.3	59.3 ± 11.5	57.5 ± 10.6	0.042
Men	7 (100%)	92 (92%)	41 (85.4%)	33 (84.6%)	0.391
Diabetes mellitus	0 (0%)	19 (19%)	13 (27.1%)	13 (33.3%)	0.124
Hypertension	3 (42.9%)	49 (49%)	28 (58.3%)	24 (61.5%)	0.454
Smoking status					0.927
Current smoker	3 (42.9%)	51 (51%)	23 (47.9%)	20 (51.3%)	
Ex-smoker	1 (14.3%)	10 (10.0%)	8 (16.7%)	4 (10.3%)	
Prior CABG	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1.000
Prior MI	2 (28.6%)	7 (7%)	3 (6.3%)	5 (12.8%)	0.159
Anterior wall infarction	4 (57.1%)	60 (60%)	28 (58.3%)	19 (48.7%)	0.407

NB: 14 (6.7%) missing data

Table II. Baseline variables by door-to-balloon time.

Baseline variables	Door-to-balloon time			
	0 to < 90 minutes (n=69)	90 to < 180 minutes (n=101)	≥ 180 minutes (n=29)	p-value
% of total patients	35%	51%	14%	N/A
Age ≤ 70 years	64 (92.8%)	83 (82.2%)	25 (86.2%)	0.141
Age (years) (mean ± SD)	54.2 ± 10.3	56.3 ± 12.6	58.9 ± 13.3	0.251
Men	65 (94.2%)	87 (86.1%)	26 (89.7%)	0.243
Diabetes mellitus	13 (18.8%)	23 (22.8%)	10 (34.5%)	0.244
Hypertension	35 (50.7%)	54 (53.5%)	15 (51.7%)	0.938
Smoking status				0.636
Current smoker	35 (50.7%)	51 (50.5%)	12 (41.4%)	
Ex-smoker	7 (10.1%)	11 (10.9%)	6 (20.7%)	
Prior CABG	0 (0%)	1 (1%)	0 (0%)	1.000
Prior MI	3 (4.3%)	9 (8.9%)	6 (20.7%)	0.036
Anterior wall infarction	34 (49.3%)	62 (61.4%)	18 (62.1%)	0.300

NB: 9 (4.3%) missing data

minutes versus ≥ 90 minutes, was performed by adjusting for symptom-to-balloon time.

RESULTS

The demographical and clinical characteristics of 208 patients by time-to-balloon are shown in Tables I and II. The ethnic composition of patients was Chinese (65%), Indian (18%), Malay (15%) and others (2%). Patients were predominantly male (89%) and aged younger than 70 years (86%). The majority of patients were presented directly to NUH (87%), with transfers from TTSH (10%) and AH (3%) making up the balance. Two-thirds of patients (65%) arrived at the hospitals during regular office hours.

The median symptom-to-balloon and door-to-balloon times were 3 hours 55 minutes and 110 minutes, respectively (Figs. 1–2). Only 3.6% of patients achieved a time to reperfusion of less than two hours after symptom onset. 34.7% of patients achieved a door-to-balloon time of less than 90 minutes. Patients with longer ischaemic times were older, more often suffering from diabetes mellitus and hypertension. Cardiogenic shock was present in 16 (7.7%) patients. The vessels responsible for acute STEMI were the left anterior descending artery (57%), right coronary artery (34%) and circumflex artery (9%). Adjuvant therapeutics administered included coronary stenting (97%), glycoprotein IIb/IIIa inhibitors (47%), thrombectomy device (40%) and distal protection device (10%).

Table III. One- and six-month clinical outcomes.

Variables	Symptom-to-balloon time				
	< 120 minutes (n=7)	120–240 minutes (n=100)	240–360 minutes (n=48)	> 360 minutes (n=39)	p-value
One month					
Death	0	6 (6.2%)	5 (10.6%)	5 (12.8%)	0.250
MACE	0	6 (6.2%)	5 (10.6%)	6 (15.4%)	0.318
Six months					
Death	0	8 (8.5%)	5 (11.1%)	6 (15.8%)	0.556
MACE	0	9 (9.6%)	8 (17.8%)	9 (23.7%)	0.115
	Door-to-balloon time				
	0 to < 90 minutes (n=69)	90 to < 180 minutes (n=101)	> 180 minutes (n=29)		p-value
One month					
Death	3 (4.4%)	9 (9.2%)	5 (17.2%)		0.119
MACE	3 (4.4%)	10 (10.2%)	5 (17.2%)		0.121
Six months					
Death	3 (4.5%)	10 (10.5%)	7 (25%)		0.013
MACE	5 (7.6%)	14 (14.7%)	8 (28.6%)		0.029

Table IV. One- and six-month clinical outcomes by symptom-to-balloon time.

	Symptom-to-balloon time			
		Mean (SD) (hours)	Odds-ratio (95% CI)	p-value*
One month				
Death	Yes	5.06 (2.48)	1.20 (0.88, 1.64)	0.250
	No	4.86 (3.26)		
MACE	Yes	6.08 (4.81)	1.45 (1.09, 1.92)	0.011
	No	4.76 (2.99)		
Six months				
Death	Yes	4.96 (2.40)	1.03 (0.70, 1.53)	0.867
	No	4.85 (3.28)		
MACE	Yes	5.92 (4.16)	1.19 (1.01, 1.41)	0.046
	No	4.68 (2.98)		

*Covariates adjusted

Mortalities at one and six months were 8.2% and 9.6%, respectively, while MACE at one and six months were 8.7% and 13.0%, respectively. The one-month mortality reduced to 4.7% if cardiogenic shock patients were excluded. Mortality and MACE rates were both consistently escalating with longer symptom-to-balloon and door-to-balloon times (Table III) despite not achieving statistical significance. A longer symptom-to-balloon time was a significant predictor of MACE events at one month (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.09–1.92; p = 0.011) and six months (OR, 1.19; 95% CI 1.01–1 .41; p = 0.046) but not mortality, after adjusting for baseline confounding variables (Tables IV and V). Door-to-balloon time, however, did not demonstrate any statistically significant impact on outcomes after logistic regression. Baseline covariates incorporated in the multivariate analyses included age, multivessel disease and cardiogenic shock.

Additional analysis by examining the impact of different door-to-balloon time of < 90 minutes versus ≥ 90 minutes within the same symptom-to-balloon time revealed no significant difference for one-month mortality (OR, 1.22; 95% CI, 0.05–29.25; p = 0.902), six-month mortality (OR, 2.66; 95% CI, 0.16–43.27; p=0.493), one-month MACE (OR, 2.02; 95% CI, 0.10–40.87, p = 0.648) and six-month MACE (OR, 2.28; 95% CI, 0.49–10.67; p=0.294).

Table V. One- and six-month cumulative clinical outcomes by door-to-balloon time.

	Door-to-balloon time			
		Mean (SD) (minutes)	Odds-ratio (95% CI)	p-value*
One month				
Death	Yes	141.88 (71.81)	1.00 (0.98, 1.02)	0.728
	No	121.67 (60.11)		
MACE	Yes	142.17 (69.68)	1.00 (0.98, 1.02)	0.711
	No	121.53 (60.25)		
Six months				
Death	Yes	149.80 (74.72)	1.01 (0.98, 1.03)	0.639
	No	120.49 (59.59)		
MACE	Yes	141.32 (74.16)	1.01 (0.99, 1.02)	0.082
	No	119.49 (59.13)		

*Covariates adjusted

DISCUSSION

The main finding of our study is that among patients with STEMI undergoing modern mechanical reperfusion, delay in time from symptom onset to balloon is an important predictor of poor outcome. The association between increased duration of coronary vessel occlusion and degree of myocardial necrosis has been well characterised in animal models.[7] Therefore, late reperfusion is expected to result in poor flow, less myocardial salvage and thus suboptimal cardiovascular outcomes, even after optimal mechanical reperfusion. In other words, the extent of infarct size could be reduced significantly if the occlusion was interrupted and coronary blood flow restored.

However, Zijlstra et al[8] reported that mortality increased linearly with time delay only in patients treated with fibrinolytics, whereas it was relatively stable in patients treated by primary angioplasty. This surprise finding could potentially be explained by the fact that only 50%–60% of patients treated with fibrinolytic agents achieved the important end-point of angiographically normal flow,[9,10] compared to 93%–96% of patients treated with primary PCI.[11,12] Nevertheless, evidence is gradually mounting that time to reperfusion is just as important in primary angioplasty, as it is in fibrinolytic therapy.[6,13,14] In our cohort of 208 patients with STEMI undergoing primary angioplasty, our findings support the prognostic role of early restoration of myocardial perfusion.

The fact that only 3.6% of patients achieved a symptom-to-balloon time of less than two hours raised the need for further awareness and education. Merely 35% of our patients achieved a door-to-balloon time of less than 90 minutes in accordance to the recommendation of American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of AMI.[15] These findings highlight the many opportunities in our current myocardial infarction management pathway that can be improved. The importance of public education to facilitate the early recognition of alarming cardiac symptoms could not be emphasised more.

Our finding that two-thirds of patients presented during office hours (0800 to 1700, Mondays to Fridays, 0800 to 1230 Saturdays) suggests the possibility that late presentation may have occurred as a consequence of inaccessibility to medical facilities during after hours and weekends. This factor could have partially contributed to considerable delay in the recognition of AMI. Despite not reaching statistical significance, our results demonstrate consistent increased mortality and MACE with longer delays for both symptom-to-balloon and door-to-balloon times (Table III). The strong correlation would translate into a likely positive association for both variables in predicting AMI outcomes. In addition, both symptom-to-balloon and door-to-balloon times did not predict mortality after adjustment for significant covariates in our study (Tables IV and V). Nonetheless, symptom-to-balloon time has shown positive association with MACE at both one and six months. These findings are most likely explained by the limitation of a small sample size with low mortality rates. A larger sample size may be required to attain the power for differences to be detected. The major limitation of our study is the subjective and retrospective nature of symptom onset time as reported by our patients. Besides, the reported times of symptom onset were subjected to uncertainties in view of the language barriers in a multiracial society as Singapore. Missing data were 6.7% and 4.3% for symptom-to-balloon and door-to-balloon times, respectively.

Reducing symptom-to-door and door-to-balloon times can shorten symptom-to-balloon time. Educating both the

public and healthcare providers (e.g. general practitioners, triage nurses, paramedics) is paramount in minimising delay in both times. Regular community symposiums to promote public awareness of common cardiac symptoms have been an overlooked strategy where additional efforts are critically required. The implementation of a more efficient clinical pathway to shorten the hospital triage process would be useful. Pre-hospital triage can begin at home or in the ambulance to facilitate early recognition of STEMI. Rapid ambulance transport and early pretreatment with pharmacological agents before primary angioplasty are other strategies that could shorten delays in time to primary PCI. Other emerging strategies include the administration of pharmacological agents to facilitate the opening of occluded arteries in transition to PCI ("facilitated" PCI).[16,17] Pharmacological agents that are currently evaluated in clinical trials include glycoprotein (GP) IIb/IIIa inhibitors, fibrinolytic agents or the pre-procedural administration of a combination of GP IIb/IIIa inhibitors and reduced doses of fibrinolytic agents.

In conclusion, early presentation of patients with STEMI to hospitals is associated with significantly lower rate of MACE. Improving public awareness and the accessibility of health services to patients are essential to reducing poor outcomes. It is imperative that physicians, hospitals, and healthcare systems work together in a collaborative fashion to reduce symptom-to-balloon time.

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REFERENCES

1. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996; 348:771-5. Comment in: ACP J Club 1996; 126:31. Lancet 1996; 348:1312-3.
2. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994; 343:311-22. Erratum in: Lancet 1994; 343:742. Comment in: Lancet 1994; 343:912. Lancet 1994; 343:912-3. Lancet 1994; 343:1225-6. Lancet 2001; 357:1367-8.
3. Newby LK, Rutsch WR, Califf RM, et al. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996; 27:1646-55.
4. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. JAMA 2000; 283:2941-7. Comment in: JAMA 2000; 283:2988-9. JAMA 2001; 285:1701; author reply 1701-2.
5. Brodie BR, Stuckey TD, Wall TC, et al. Importance of time to reperfusion for 30-day and late survival and recovery of left ventricular function after primary angioplasty for acute myocardial infarction. J Am Coll Cardiol 1998; 32:1312-9.
6. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004; 109:1223-
5. Comment in: Circulation 2004;109:1806-8.
7. Reimer KA, Lowe JE, Rasmussen MM, Jennings RB. The wavefront phenomenon of ischemic cell death. I: Myocardial infarct size vs duration of coronary occlusion in dogs. Circulation 1977; 56:786-94.
8. Zijlstra F, Patel A, Jones M, et al. Clinical characteristics and outcome of patients with early (<2 h), intermediate (2-4 h), and late (>4 h) presentation treated by primary coronary angioplasty or thrombolytic therapy for acute myocardial infarction. Eur Heart J 2002; 23:550-7. Comment in: Eur Heart J 2002; 23:1146-8.
9. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; 329:673-82. Comment in: ACP J Club 1994; 120 suppl 2:33. N Engl J Med 1993; 329:723-5. N Engl J Med 1994; 330:504; author reply 505-6. N Engl J Med 1994;330:505; author reply 505-6. N Engl J Med 1994; 331:277-8. N Engl J Med 1998; 338:545-6; author reply 546-7.
10. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993; 329:1615-22. Erratum in: N Engl J Med 1994; 330:516. Comment in: N Engl J Med 1993; 329:1650-2. N Engl J Med 1994; 330:1089; author reply 1089-90.
11. Mehta RH, Harjai KJ, Cox D, et al. Clinical and angiographic correlates and outcomes of suboptimal coronary flow inpatients with acute myocardial infarction undergoing primary percutaneous coronary intervention. J Am Coll Cardiol 2003; 42:1739-46.
12. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. N Engl J Med 2002; 346:957-66. Comment in: N Engl J Med 2002; 347:367-8; author reply 367-8. N Engl J Med 2002; 346:954-5.
13. Gibson CM, de Lemos JA, Antman EM; TIMI Study Group. Time is muscle in primary PCI: the strength of the evidence grows. Eur Heart J 2004; 25:1001-2. Comment on: Eur Heart J 2004; 25:1009-13.
14. De Luca G, van't Hof AW, de Boer MJ, et al. Time-to-treatment significantly affects the extent of ST-segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. Eur Heart J 2004; 25:1009-13. Comment on: Eur Heart J 2004; 25:1001-2.
15. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. J Am Coll Cardiol 2004; 44:671-719. Erratum in: J Am Coll Cardiol 2005; 45:1376. Comment in: J Am Coll Cardiol 2005; 45:1551. J Am Coll Cardiol 2005; 45:1552; author reply 1552-3.
16. Antman EM, Van de Werf F. Pharmacoinvasive therapy: the future of treatment for ST-elevation myocardial infarction. Circulation 2004; 109:2480-6.
17. Dauerman HL, Sobel BE. Synergistic treatment of ST-segment elevation myocardial infarction with pharmacoinvasive recanalization. J Am Coll Cardiol 2003; 42:646-51.