Troponin T elevation and prognosis after multivessel compared with single-vessel elective percutaneous coronary intervention

M.B. Nienhuis, J.P. Ottervanger, J.-H.E. Dambrink, L.D. Dikkeschei, H. Suryapranata, A.W.J. van 't Hof, J.C.A. Hoorntje, M.J. de Boer, A.T.M. Gosselink, F. Zijlstra

Background. Although techniques for percutaneous coronary intervention (PCI) have improved, patients with PCI of more vessels may still have an increased risk. We performed a prospective observational study evaluating the differences between multivessel and single-vessel procedures according to postprocedural troponin T (TnT) elevation and events during follow-up.

Methods. The study included 713 patients without elevated TnT (<0.05 ng/ml) before PCI. Primary endpoint was the combined endpoint of death, myocardial infarction, stroke, repeat coronary angiography and readmission for anginal symptoms during the mean follow-up of 10.9 months. **Results.** TnT after PCI was elevated in 150 patients (21%) and was significantly associated with an increased incidence of the primary endpoint (RR 1.55, 95% CI 1.01 to 2.38). PCI of more than one vessel was performed in 146 patients (20%). These patients more often had increased TnT levels after the procedure (31.5 vs. 18.3%, $p=0.001$) and an increased incidence of the primary endpoint during follow-up (28 vs. 19%, $p=0.01$). After multi-

variable analysis, multivessel PCI was a statistically significant predictor of postprocedural TnT increase (OR 1.90, 95% CI 1.17 to 3.06). Multivessel PCI was also associated with an increased risk of the primary endpoint (OR 1.73, 95% CI 1.18 to 2.52), but after adjusting for multivessel disease this association was not statistically significant (OR 1.42, 95% CI 0.92 to 2.19).

Conclusion. Elective PCI of more vessels in one session is, in comparison with single-vessel PCI, more often associated with postprocedural troponin T rise and a (nonsignificantly) higher incidence of cardiac events during follow-up. Whether staged PCI is associated with less morbidity has to be assessed. (*Neth Heart J* 2007;15:178-83.)

Keywords: percutaneous coronary interventions, revascularisation, troponin, multivessel

During the last decade, percutaneous coronary intervention (PCI) has been improved.¹ Use of (drug-eluting) stents has decreased the occurrence of restenosis. Furthermore, PCI is now often combined with diagnostic coronary angiography in one procedure.^{2,3} Another development is performing multivessel PCI in one session. Although it was not confirmed by a recently published registry,⁴ randomised trials have suggested that in most patients with multivessel disease, PCI is comparable to coronary artery bypass grafting (CABG) with regards to mortality and myocardial infarction (MI) in follow-up.⁵ Performing more interventions in one procedure may be faster and more convenient than staged procedures. Although one study suggests that this one-session strategy might be more harmful, there are only few data on this issue.⁶

After elective PCI, up to 30% of patients develop elevated cardiac specific troponin T (TnT) even when the procedure is considered successful and uncomplicated. Such elevations of TnT have been associated with an increased incidence of future cardiac events.⁷⁻¹¹

M.B. Nienhuis
J.P. Ottervanger
J.-H.E. Dambrink
H. Suryapranata
A.W.J. van 't Hof
J.C.A. Hoorntje
M.J. de Boer
A.T.M. Gosselink

Department of Cardiology, Isala Clinics, Zwolle, the Netherlands

L.D. Dikkeschei

Department of Clinical Chemistry, Isala Clinics, Zwolle, the Netherlands

F. Zijlstra

Department of Cardiology, University Medical Centre Groningen, Groningen, the Netherlands

Correspondence to: J.P. Ottervanger
Department of Cardiology, Isala Clinics, PO Box 10500, 8000 GM Zwolle, the Netherlands
Email: v.r.c.derks@isala.nl

The current prospective study was designed to evaluate the effect of multivessel PCI versus single-vessel PCI on the incidence of troponin T (TnT) elevation after elective PCI and the occurrence of cardiac events during follow-up.

Materials and Methods

Study population

This was a prospective, observational study.¹¹ The patient cohort included unselected patients who underwent elective PCI in Isala Clinics, Zwolle, the Netherlands between June 2002 and August 2003. All patients had symptomatic coronary artery disease with objective evidence of ischaemia.

Patients with single-vessel as well as patients with multivessel disease were included. Multivessel disease was defined as more than 50% stenosis in two or more major coronary arteries. The cardiologist and cardiac surgeon (heart team) determined whether culprit lesion interventions only or multivessel interventions for multiple lesions in more than one vessel were indicated in patients with multivessel disease. Patients with acute coronary syndrome (ACS) were excluded.

Procedure and laboratory testing

All PCI procedures were performed according to the standard protocol. Routine care before and after the procedure was undertaken for all patients, including preprocedural use of aspirin and a bolus of intravenous heparin (5000 U) at the beginning of the procedure. Patients not on clopidogrel (approximately 50%) received a loading dose of 300 mg clopidogrel just before the procedure. Postprocedure, all patients were treated with clopidogrel 75 mg once daily for at least 28 days. Use of GP IIb-IIIa inhibitors or stents was at the discretion of the interventional cardiologist. At the time the study was performed, the use of drug-eluting stents was less than 10%.

A blood sample was routinely obtained from all patients just before the interventional procedure in the catheterisation room. The second sample was taken the day after, approximately 12 hours after the procedure. All samples were prepared and stored locally in our core laboratory at -70°C until analysed. The medical practitioners were blinded for the results of this analysis.

TnT was analysed using the third-generation troponin T test (Roche diagnostics, Mannheim, Germany) with a threshold of 0.01 ng/ml. Although the 99th percentile of normal TnT may be as low as 0.01 ng/ml, in accordance with other recent studies we used 0.05 ng/ml as cut-off value.¹²⁻¹⁴

Endpoints

The primary endpoint was the combined incidence of readmission because of angina, repeat coronary angiography, repeat revascularisation, MI, stroke and death. The second primary endpoint was TnT elevation

after PCI. Clinical outcomes were obtained at least 30 days after PCI by telephone interviews with the patient, their relatives or their cardiologist or primary physician. Information on clinical events was noted using a standardised format. All clinical events were obtained from the medical files. New onset of Q waves or CK and CK-MB above cut-off values was used as the definition of MI during follow-up. All deaths during follow-up were considered to be of cardiac causes.

Statistical analysis

All analyses were performed with SPSS statistical software (SPSS Inc., Chicago, Illinois).

Group comparisons were done by the χ^2 test for proportions and Student's t test for continuous variables.

Multivariable analyses by logistic regression were performed to assess the independent association between multivessel PCI and increased TnT after the PCI. Multivariate Cox proportional hazards regression analysis was applied to describe the independent relation between multivessel PCI and the occurrence of the primary endpoint during follow-up. A probability value of $p < 0.05$ was considered significant.

Results

During the enrolment period, 745 patients were screened for our study. Of these patients, a total of 713 (96%) did not have elevated TnT (< 0.05 ng/ml) before the PCI, representing the final study group. Mean age was 64 years (range 35 to 87 years), 211 patients (30%) were female, 127 patients (18%) had diabetes and 111 patients (16%) had angina with Canadian Cardiovascular Society (CCS) class 4. A total of 501 patients (70%) were treated with a stent. Multivessel disease was present in 381 patients (53%), which was documented before the PCI procedure in 344 patients (90%). PCI of more than one vessel was performed in 146 patients (20%). Differences between patients with multivessel PCI and PCI of one vessel are summarised in table 1. It is shown that there are no major differences between the two patient groups.

Baseline characteristics of the 381 patients in the subgroup with multivessel disease did not differ essentially from the entire study group of 713 patients. There were only a few differences between patients undergoing multivessel and single-vessel PCI in this subgroup. Patients with previous CABG less often had multivessel PCI (8 vs. 24%, $p < 0.001$), whereas previous PCI (31 vs. 26%) and MI in the history (50 vs. 49%) were not significantly different. Furthermore, patients with PCI of the right coronary artery significantly more often had multivessel PCI (37 vs. 26%, $p = 0.03$).

In patients with multivessel disease, postprocedural troponin elevation occurred significantly more often in patients undergoing multivessel PCI compared with single-vessel PCI (32 vs. 20%, $p = 0.008$). However, multivessel PCI was neither significantly associated

Table 1. Characteristics of 713 patients: multivessel procedure versus single-vessel procedure.

Variables	Multivessel PCI (n=146)	Single-vessel PCI (n=567)	P
Age, years (SD)	64.1 (10.3)	63.4 (10.4)	0.46
Female, n (%)	45 (31)	166 (29)	0.72
Risk factors			
- Diabetes mellitus, n (%)	27 (18)	100 (18)	0.82
- Hypercholesterolaemia, n (%)	84 (58)	314 (55)	0.11
- Smoking, n (%)	42 (29)	188 (33)	0.31
- Hypertension, n (%)	69 (47)	242 (43)	0.15
- Family history of CAD, n (%)	60 (41)	190 (34)	0.08
- CCS4 before PCI, n (%)	23 (16)	88 (16)	0.95
Medical history			
- Myocardial infarction, n (%)	73 (50)	246 (43)	0.16
- PCI, n (%)	45 (31)	144 (25)	0.19
- CABG, n (%)	11 (8)	73 (13)	0.07
- Stroke, n (%)	14 (10)	37 (7)	0.20
Following PCI			
- Death, n (%)	0	9 (2)	0.13
- Combined endpoint, n (%)	39 (27)	100 (18)	0.014
- Postprocedural troponin elevation, n (%)	46 (32)	104 (18)	0.001

PCI=percutaneous coronary intervention, CAD=coronary artery disease, CCS=Canadian cardiovascular society classification, CABG=coronary artery bypass graft.

Table 2. Baseline characteristics of 713 patients according to troponin increase (>0.05 ng/ml) after elective PCI.

Variables	Troponin not increased (n=563)	Troponin increased (n=150)	P
Age, years (SD)	63.5 (10)	63.7 (11)	0.84
Female, n (%)	172 (31)	39 (26)	0.28
Risk factors			
- Diabetes mellitus, n (%)	108 (19)	19 (13)	0.06
- Hypercholesterolaemia, n (%)	316 (69)	82 (68)	0.94
- Smoking, n (%)	179 (33)	51 (35)	0.61
- Hypertension, n (%)	249 (49)	62 (48)	0.80
- Family history of CAD, n (%)	195 (37)	55 (40)	0.59
- Multivessel disease, n (%)	289 (51)	92 (61)	0.03
Medical history			
- Myocardial infarction, n (%)	249 (44)	70 (47)	0.56
- PCI, n (%)	148 (26)	41 (27)	0.81
- CABG, n (%)	68 (12)	16 (11)	0.63
- Stroke, n (%)	38 (6.7)	13 (8.7)	0.42
PCI			
- RCA, n (%)	165 (29)	35 (23)	0.15
- LAD, n (%)	239 (43)	60 (40)	0.59
- Multivessel PCI, n (%)	100 (18)	46 (31)	0.001
- Stent, n (%)	395 (70)	106 (72)	0.73
CCS4, n (%)	81 (14)	30 (20)	0.09

CAD=coronary artery disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, RCA=right anterior descending, LAD=left anterior descending, CCS=Canadian cardiovascular society classification.

with mortality in follow-up, nor with the primary combined clinical endpoint in this selected group (27 vs. 21%, $p=0.19$).

TnT was elevated after the PCI in 150 patients of the total study population (21%). All baseline variables according to elevated troponin after the PCI are shown in table 2. Multivessel disease and multivessel PCI were both significantly associated with increased TnT rise after PCI ($p=0.001$). The unadjusted odds ratio (OR) for increased TnT after multivessel PCI was 2.1 (95% CI 1.4 to 3.1). After multivariable analyses, adjusting for age, gender, diabetes, CCS classification and multivessel disease, multivessel PCI (OR 1.9, 95% CI 1.17 to 3.06), but not multivessel disease (OR 1.17, 95% CI 0.76 to 1.8) was significantly associated with increased TnT after the PCI.

Thirty days of follow-up was available in all patients, mean total follow-up was 10.9 months (SD 10.6). Long-term mortality was low (1.3%) and associated with neither multivessel PCI nor TnT elevation after PCI. The occurrence of the combined endpoint death and/or MI in follow-up was also low and not related to troponin release (2.1% (12/563) for patients with nonelevated troponin vs. 4.0% (6/150) for patients with elevated troponin, NS). Patients with multivessel

PCI more often underwent recurrent PCI (19 patients, 13.0%) compared with single-vessel PCI (39 patients, 6.9%, $p=0.016$).

During the follow-up period, the primary combined endpoint was observed in 139 patients (19.5%): nine patients died (two of noncardiac, seven of cardiac or unknown causes), eight patients had an MI and 64 underwent recurrent revascularisation (49 PCI, 6 CABG, 9 PCI and CABG). Furthermore, seven patients had a stroke, 36 patients underwent re-angiography and another 15 patients were readmitted for anginal symptoms.

Differences between patients with and without a primary endpoint during the follow-up period are shown in table 3. An increased risk of occurrence of the primary endpoint was observed in patients with diabetes, in patients with a PCI or CABG in their history, in patients with multivessel disease and in patients with an increased TnT after PCI. Also patients with PCI of more vessels had significantly more events during follow-up, with the unadjusted odds ratio 1.7 (95% CI 1.2 to 2.5). After adjusting for differences in age, gender, diabetes and CCS classification, multivessel PCI had an increased incidence of the primary endpoint (OR 1.73, 95% CI 1.18 to 2.52). However, if multivessel disease was also included in the multi-

Table 3. Baseline characteristics of 713 patients according to cardiac events* during follow-up.

Variables	Patients with events (n=139)	Patients without events (n=574)	P
Age, years (SD)	64.9 (± 10.3)	64.9 (± 10.3)	0.8
Female, n (%)	46 (33)	165 (29)	0.31
Risk factors			
- Diabetes mellitus, n (%)	40 (29)	87 (15)	0.01
- Hypercholesterolaemia, n (%)	85 (72)	313 (68)	0.37
- Smoking, n (%)	39 (29)	191 (34)	0.24
- Hypertension, n (%)	65 (51)	246 (49)	0.59
- Family history of CAD, n (%)	50 (39)	200 (38)	0.70
- Multivessel disease, n (%)	88 (63)	293 (51)	0.009
Medical history			
- Myocardial infarction, n (%)	67 (48)	252 (44)	0.38
- PCI, n (%)	61 (44)	128 (22)	0.001
- CABG, n (%)	26 (19)	58 (10)	0.005
- Stroke, n (%)	4 (2.9)	47 (8.2)	0.03
PCI			
- RCA, n (%)	39 (28)	161 (28)	1.0
- LAD, n (%)	54 (39)	245 (43)	0.41
- Multivessel PCI, n (%)	39 (28)	107 (19)	0.01
- Stent, n (%)	97 (70)	404 (71)	0.85
CCS4, n (%)	20 (14)	91 (16)	0.67
Troponin increase after PCI, n (%)	38 (27)	112 (19.5)	0.04

CAD=coronary artery disease, PCI=percutaneous coronary intervention, CABG=coronary artery bypass graft, RCA=right anterior descending, LAD=left anterior descending, CCS=Canadian cardiovascular society classification. *Primary endpoint: readmission, repeat coronary angiography, repeat PCI, CABG, MI, stroke and death.

variable model, the association was not statistically significant (OR 1.42, 95% CI 0.92 to 2.19).

Discussion

Multivessel PCI was, in comparison with single-vessel procedure, significantly associated with more frequent postprocedural TnT release. Multivessel PCI was also associated with an increased incidence of cardiac events during the follow-up period, but this could in part be explained by the multivessel disease itself. Mortality in this low-risk population was low and not associated with multivessel PCI.

In patients undergoing elective multivessel PCI, there are conflicting results about the safety and long-term results. One study reported similar clinical outcomes for patients undergoing multivessel PCI when compared with patients undergoing single-vessel PCI.¹⁵ Others report comparable events in follow-up for both groups, except for re-PCI, occurring more frequently in patients undergoing multivessel PCI.^{16,17}

IJsselmuiden et al. randomised 219 patients with multivessel disease to complete vs. culprit vessel PCI, resulting in similar major adverse cardiac events at follow-up and similar total costs after one year in the two groups.¹⁸ Recently, it was observed that in patients scheduled for multivessel PCI, interventions of haemodynamically nonsignificant stenoses can be safely deferred, based on fractional flow reserve (FFR) measurements.¹⁹

In an analysis of the TARGET study, multivessel PCI was, when compared with single-vessel PCI, more often associated with events in follow-up, primarily due to an increase in periprocedural MI.²⁰ However, one important, but not reported baseline characteristic was the presence of multivessel disease, which might have influenced the results.

Other studies reported a relation between periprocedural myocardial injury and multivessel PCI.^{21,22} Only one study compared staging of multivessel PCI with the one-procedure approach,⁶ with a nonsignificant trend that patients in the staged group had less cardiac events ($p=0.08$). This trend was mainly the result of a lower need for reinterventions.

In the setting of ST-elevation MI, it is as yet unknown whether treatment of only the infarct-related artery is superior to multivessel intervention.^{23,24}

Troponin release after elective PCI occurs in approximately 30% of patients and has been related to several patient-related factors, including multivessel coronary artery disease, older age, interventions of de-novo lesions, saphenous vein graft interventions and complex lesions.²² Also procedure-related factors may be of importance, such as the no-reflow phenomenon, distal embolisation and side branch occlusion.²⁵

Since troponin release is associated with several procedure-related factors, it is not surprising that performing PCI in more than one vessel during the same procedure is (also in our study) more often associated

with troponin release after PCI. This can be explained by several mechanisms. First, it has been demonstrated that postprocedural enzyme release relates to intra-procedural reduction of plaque volume, pointing towards the significance of atheroembolisation in periprocedural myocardial injury.²⁶ Therefore, PCI of more vessels, reducing more plaque volume, may more often result in significant enzyme release.

Second, in vivo plaque disruption by PCI causes shedding of potent biofactors such as tissue factor into the coronary circulation, leading to microvascular thrombosis and no-reflow.²⁷ This thrombogenic state can influence the result of additional PCI procedures in the same setting. Third, as PCI directly results in activation of the sympathetic nervous system, which in turn results in diffuse vasoconstriction²⁸ every additional PCI performed can result in extra troponin release.

Staging of the PCI by first performing a single-vessel procedure, followed weeks or months later by an additional procedure, might result in less troponin release and less cardiac events, although this has not yet been proven. More frequent use of FFR may prevent unnecessary PCI.

The presented study has some limitations. First, it is an observational study and differences between patients with and without multivessel disease could have influenced the results. Second, because mortality and MI in this group are low, the primary combined endpoint consisted of a number of different endpoints. These endpoints may be considered as weak, but an important reason for performing elective PCI is to improve quality of life. Knowing the low risk of events after elective PCI in stable patients and realising readmission and repeat angiography are 'events' in the patients point of view, these two endpoints were also included in the primary combined endpoint. Third, the number of patients was relatively small. Together with the low mortality during follow-up, no association could be demonstrated between multivessel PCI, TnT release and mortality, although it is not excluded that this relation does exist. As a consequence of the relatively low number of patients and particularly the low event rate, additional subgroup analyses, for example stratifying to the magnitude of troponin release, were not possible. Fourth, the use of drug-eluting stents was low. Although this probably will not have influenced data on troponin release, it might have influenced the follow-up data, especially the need for recurrent revascularisation. Fifth, approximately 50% of our patients were not on clopidogrel before the PCI and received the drug just before the procedure. This could have influenced the results, because the protective effect of clopidogrel is stronger when it is given several hours or more before the procedure.²⁹ Sixth, no routine angiographic follow-up was available for our patient cohort. Finally, as a routine electrocardiogram was not collected in the follow-up period, the number of MIs in follow-up could have been underestimated.

Conclusion

When compared with single-vessel procedure, a multivessel PCI procedure is associated with more TnT release. Furthermore, there is a trend towards a higher incidence of cardiac events during follow-up after a multivessel procedure. Whether a staged approach in patients with multivessel disease is associated with less events during follow-up has to be assessed. ■

References

- 1 Lenzen MJ, Boersma E, Bertrand ME, Maier W, Moris C, Piscione F, et al. European Society of Cardiology. Management and outcome of patients with established coronary artery disease: the Euro Heart Survey on coronary revascularization. *Eur Heart J* 2005;**26**:1169-79.
- 2 Kimmel SE, Berlin JA, Hennessy S, Strom BL, Krone RJ, Laskey WK. Risk of major complications from coronary angioplasty performed immediately after diagnostic coronary angiography: results from the Registry of the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 1997;**30**:193-200.
- 3 Goldstein CL, Racz M, Hannan EL. Impact of cardiac catheterization-percutaneous coronary intervention timing on in-hospital mortality. *Am Heart J* 2002;**144**:561-7.
- 4 Hannan EL, Racz MJ, Walford G, Jones RH, Ryan TJ, Bennett E, et al. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005;**352**:2174-83.
- 5 Smith SC, Feldman TE, Hirshfeld Jr JW, Jacobs AK, Kern MJ, King III SB, et al. ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. A report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2006;**113**:156-75.
- 6 Nikolsky E, Halabi M, Roguin A, Zdrovnyak A, Gruberg L, Hir J, et al. Staged versus one-step approach for multivessel percutaneous coronary interventions. *Am Heart J* 2002;**143**:1017-26.
- 7 Wu AH, Boden WE, McKay RG. Long-term follow-up of patients with increased cardiac troponin concentrations following percutaneous coronary intervention. *Am J Cardiol* 2002;**89**:1300-2.
- 8 Nienhuis MB, Ottervanger JP, Bilo HJG, Dikkeschei LD, Zijlstra F. Prognostic value of troponin after elective percutaneous coronary intervention: A Meta-Analysis. Submitted.
- 9 Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr, Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. *J Am Coll Cardiol* 2006;**48**:1765-70.
- 10 Nageh T, Sherwood RA, Harris BM, Thomas MR. Prognostic role of cardiac troponin I after percutaneous coronary intervention in stable coronary disease. *Heart* 2005;**91**:1181-5.
- 11 Nienhuis MB, Ottervanger JP, Dikkeschei LD, Suryapranata H, de Boer MJ, Dambrink JHE, et al. Prognostic importance of elevated troponin T and creatine kinase after elective percutaneous coronary intervention. *Int J Cardiol*, in press.
- 12 Jordanova N, Gyongyosi M, Khorsand A, Falkensammer C, Zorn G, Wojta J, et al. New cut-off values of cardiac markers for risk stratification of angina pectoris. *Int J Cardiol* 2005;**99**:429-35.
- 13 Solymoss BC, Bourassa MG, Fortier A, Theroux P. Evaluation and risk stratification of acute coronary syndromes using a low cut-off level of cardiac troponin T, combined with CK-MB mass determination. *Clin Biochem* 2004;**37**:286-92.
- 14 Collinson PO, Stubbs PJ, Kessler AC. Multicentre Evaluation Of Routine Immunoassay Of Troponin T Study. Multicentre evaluation of the diagnostic value of cardiac troponin T, CK-MB mass, and myoglobin for assessing patients with suspected acute coronary syndromes in routine clinical practice. *Heart* 2003;**89**:280-6.
- 15 Kornowski R, Mehran R, Satler LF, Pichard AD, Kent KM, Greenberg A, et al. Procedural results and late clinical outcomes following multivessel coronary stenting. *J Am Coll Cardiol* 1999;**33**:420-6.
- 16 Kloeter UC, Jander NG, Buser PT, Osswald S, Mueller-Brand J, Pfisterer ME. Long-term outcome of angioplasty for multivessel coronary disease: importance and price of complete revascularization. *Int J Cardiol* 2001;**79**:197-205.
- 17 Goldman LE, Okrainec K, Eisenberg MJ, Schechter D, Lefkowitz J, Goudreau E, et al; ROSETTA Investigators. Six-month outcomes after single- and multi-lesion percutaneous coronary intervention: results from the ROSETTA registry. *Can J Cardiol* 2004;**20**:608-12.
- 18 IJsselmuiden AJ, Ezechiels J, Westendorp IC, Tijssen JG, Kiemeneij F, Slagboom T, et al. Complete versus culprit vessel percutaneous coronary intervention in multivessel disease: A randomized comparison. *Am Heart J* 2004;**148**:467-74.
- 19 Berger A, Botman KJ, MacCarthy PA, Wijns W, Bartunek J, Heyndrickx GR, et al. Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel disease. *J Am Coll Cardiol* 2005;**46**:438-42.
- 20 Shishehbor MH, Topol EJ, Mukherjee D, Hu T, Cohen DJ, Stone GW, et al; TARGET Investigators. Outcome of multivessel coronary intervention in the contemporary percutaneous revascularization era. *Am J Cardiol* 2006;**97**:1585-90.
- 21 Abdelmeguid AE, Topol EJ, Whitlow PL, Sapp SK, Ellis SG. Significance of mild transient release of creatine kinase-MB fraction after percutaneous coronary interventions. *Circulation* 1996;**94**:1528-36.
- 22 Natarajan MK, Kreatsoulas C, Velianou JL, Mehta SR, Pericak D, Goodhart DM. Incidence, predictors, and clinical significance of troponin-I elevation without creatine kinase elevation following percutaneous coronary interventions. *Am J Cardiol* 2004;**93**:750-3.
- 23 Corpus RA, House JA, Marso SP, Grantham JA, Huber KC Jr, Laster SB, et al. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. *Am Heart J* 2004;**148**:493-500.
- 24 Di Mario C, Mara S, Flavio A, Imad S, Antonio M, Anna P, et al. Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEPacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study. *Int J Cardiovasc Intervent* 2004;**6**:128-33.
- 25 Herrmann J. Peri-procedural myocardial injury: 2005 update. *Eur Heart J* 2005;**26**:2493-519.
- 26 Prati F, Pawlowsky T, Gil R, Labellarte A, Gziut A, Caradonna E, et al. Stenting of culprit lesions in unstable angina leads to a marked reduction in plaque burden: a major role of plaque embolization? A serial intravascular ultrasound study. *Circulation* 2003;**107**:2320-5.
- 27 Bonderman D, Teml A, Jakowitsch J, Adlbrecht C, Gyongyosi M, Sperker W, et al. Coronary no-reflow is caused by shedding of active tissue factor from dissected atherosclerotic plaque. *Blood* 2002;**99**:2794-800.
- 28 Gregorini L, Fajadet J, Robert G, Cassagneau B, Bernis M, Marco J. Coronary vasoconstriction after percutaneous transluminal coronary angioplasty is attenuated by antiadrenergic agents. *Circulation* 1994;**90**:895-907.
- 29 Nienhuis MB, Ottervanger JP, Miedema K, Suryapranata H, de Boer MJ, Dambrink JHE, et al. Pre-treatment with clopidogrel and postprocedure troponin elevation after elective percutaneous coronary intervention. *Thromb Haemost* 2006;**95**:337-40.