The use of functional tests and planned coronary angiography after percutaneous coronary revascularization in clinical practice. Results from the AFTER multicenter study

Pietro Mazzarotto [a,*], Christian Pristipino [b], Francesco Burzotta [c], Roberto Serdoz [d], Andrea Berni [e], Gennaro Sardella [f], Alessandro Danesi [g], Germano Di Sciascio [h], Leone Dino Zingales [i], Paolo Loschiavo [j], Alessandro Sciahbasi [k], Gaetano Gioffrè [l], Francesco Gemelli [a]

[a] Interventional Cardiology Unit, San Carlo Hospital, Rome, Italy
[b] Interventional Cardiology Unit, San Filippo Neri Hospital, Rome, Italy
[c] Institute of Cardiology, Catholic University, Rome, Italy
[d] Department of Cardiology, San Pietro Hospital, Rome, Italy
[e] Department of Cardiology, S. Andrea Hospital, "La Sapienza" University, Rome, Italy
[f] Department of Cardiology, Policlinico Umberto I, "La Sapienza" University, Rome, Italy
[g] Department of Cardiology, Santo Spirito Hospital, Rome, Italy
[h] Department of Cardiology, Campus Biomedico University, Rome, Italy
[i] Interventional Cardiology Unit, Belcolle Hospital, Viterbo, Italy
[j] Interventional Cardiology Unit, Sandro Pertini Hospital, Rome, Italy
[k] Department of Cardiology, Policlinico Casilino, Rome, Italy
[l] Department of Cardiology, Sant'Eugenio Hospital, Rome, Italy

Abstract

Background: The follow-up strategies after percutaneous coronary intervention (PCI) have relevant clinical and economic implications. The purpose of this prospective observational multicenter study was to evaluate the effect of clinical, procedural and organizational variables on the execution of functional testing (FT) and planned coronary angiography (CA) after PCI, and to assess the impact of American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on clinical practice.

Methods: Four hundred twenty consecutive patients undergoing PCI were categorized as class I, IIB and III indications for follow-up FT according to ACC/AHA guidelines recommendations. Furthermore, all patients were grouped according to the presence or absence of FT and/or planned CA over 12 months after PCI.

Multivariable analysis was used to assess the potential predictors of test execution.

Results: During the 12-month follow-up at least one test was performed in 72% of patients with class I indication, 63% of patients with class IIB indication and 75% of patients with class III indication (p=ns). A total of 283 patients (67%) underwent testing. The use of tests was associated with younger age (R.R. 0.94, C.I. 0.91 ± 0.97, $p<0.001$), a lower number of diseased vessels (R.R. 0.60, C.I. 0.43 ± 0.84, p=0.003), follow-up by the center performing PCI (R.R. 2.64, C.I. 1.43 ± 4.86, p=0.002), and the specific center at which PCI was performed. Most asymptomatic patients completed their testing prematurely with respect to the risk period for restenosis.

Conclusions: The use of FT and planned CA after PCI is unrelated to patient's symptom status, and depends on patient's age and logistics. ACC/AHA guidelines have no influence in clinical practice, and test timing is not tailored to the risk period for restenosis.
© 2008 Elsevier Ireland Ltd. All rights reserved.

Keywords: Percutaneous transluminal coronary angioplasty; Coronary restenosis; Heart function tests; Follow-up studies

* Corresponding author. Unità operativa di cardiologia invasiva e interventistica endovascolare, Ospedale San Carlo, Via Aurelia 275, 00165 Roma, Italy. Tel.: +39 06 39706457; fax: +39 06 39706465.
E-mail addresses: p.mazzarotto@idi.it, pietro.mazzarotto@tele2.it (P. Mazzarotto).

1. Introduction

The follow-up strategies after percutaneous coronary intervention (PCI) have relevant economic implications, may influence the patient's subsequent management and the need of further invasive procedures [1–4]. Despite that, the subgroups of patients that could take advantage from the use of functional testing (FT) or coronary angiography (CA) after PCI are not well defined. The type, number and timing of FT that should be performed are not established, as well as the discontinuation of medical treatment during tests and the duration of the follow-up program.

No specific guidelines and recommendations are provided by the European Society of Cardiology. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for PCI [5] and for cardiac radionuclide imaging [6] refer to the ACC/AHA guidelines for exercise testing [7]. The use of FT after PCI is clearly indicated (Class I) only in those patients with recurrent symptoms. It is controversial (Class II B) in selected high-risk asymptomatic patients which include patients with diabetes mellitus, multivessel disease, proximal left anterior descending coronary artery PCI, left ventricular dysfunction and suboptimal PCI result. It is not indicated (Class III) as routine strategy in asymptomatic patients. ACC/AHA guidelines for PCI [5] suggest that planned CA should be considered only in the setting of left main coronary artery PCI (Class II A). Such recommendations are supported by limited clinical evidences and result from consensus rather than prospective randomized or observational data.

Little is known about the use of FT and angiographic follow-up in the "real world". Major variations are observed, and the clinical and procedural risk profile of the patients do not seem to play a significant role in the choice of the follow-up strategy [8,9].

The Angioplasty Follow-up: Tests and Events Registry (AFTER) is a prospective multicenter registry that was conceived with the aim of describing the type, number and timing of FT after PCI, clinical and procedural profile of tested and non-tested patients, and the subsequent rate of further invasive procedures and clinical events.

The primary objectives of the current report are to evaluate the effect of clinical, procedural and organizational variables on the execution of FT or planned CA after PCI, and to assess the impact of ACC/AHA guidelines recommendations for the use of follow-up tests on clinical practice.

2. Methods

The Italian region of Lazio has 5.1 million inhabitants and is one of the most populated regions of Italy. In 2004 the area was serviced by 21 catheterization laboratories that performed a total of 8428 PCIs (official data of the Italian Society of Interventional Cardiology—www.gise.it). Twelve of those centers were involved in the AFTER study (see Appendix A). Patients undergoing PCI between November 15 and December 15 2004 were consecutively enrolled

before the procedure and were followed-up for 12 months. They were included in the registry regardless of the number and location of the lesions, the technique used for PCI and the procedural outcome. The only exclusion criteria were participation in conflicting clinical studies (such as studies with predefined follow-up), contraindications to repeat cardiac catheterization or revascularization and conditions limiting longevity with a prognosis <1 year.

In order to guarantee uniformity of data the principal investigators of the participating centers were provided with an electronic spreadsheet containing the standardized data fields to be completed for individual patients. An audit was performed on the 10th and 20th day of the enrollment time to ensure the completeness and reliability of the data. After discharge, patients who were followed-up by the participating centers were put into their standard follow-up programs, and data were directly acquired. Patients who were referred to other institutions were contacted every two months in order to obtain the documentation of FT, further invasive procedures, new symptoms, clinical events and hospitalizations. If necessary, the patient's institution or the patient's physician was contacted in order to obtain the appropriate documentation. All registered data were thoroughly checked for logical consistency and any queries were resolved with the participating centers. Finally, database entries were verified by the coordinator of the study.

Baseline demographic data, clinical indication for PCI, comorbidities, risk factors and prior revascularization procedures were registered. Angiographic and procedural data included extent of coronary artery disease, type of treated lesions (de novo, restenosis, bypass grafts), PCI technique and devices, and angiographic post-procedural result as judged by the operator. In the case of staged multivessel PCI, the last planned intervention was considered as the index procedure.

Data on FT were recorded during the 12 month follow-up. They included the reason for performing or non performing FT, the number, type (exercise test, stress-echo and radionuclide ventriculography), timing, medical therapy at test time and result. Data on repeated cardiac catheterizations were also recorded, and those CA that were scheduled at the time of PCI for invasive follow-up strategy were categorized as planned CA. Clinical events were recorded and included cardiovascular and non-cardiac death, major and minor stroke, ST-elevation and non-ST elevation myocardial infarction, percutaneous or surgical revascularizations and the occurrence of new symptoms.

Patients were grouped according to the presence or absence of at least one FT and/or planned CA over the 12-month period of observation.

In order to investigate the relationship between the risk profile as outlined by the ACC/AHA guidelines [7] and the patient's management in clinical practice, patients who remained asymptomatic after PCI were categorized as follows:

- "high-risk" patients if they had at least one of the following: diabetes, left ventricular ejection fraction less

than 40%, previous cardiac resuscitation, multivessel disease, left main or proximal left anterior descending PCI, suboptimal or failed PCI result;

- "low-risk" patients if they had none of the above features.

The study was endorsed by the Italian Society of Invasive Cardiology (SICI-GISE). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Research and Ethics Committee of the institutions involved. Written informed consent was obtained before patients were enrolled.

2.1. Statistical analysis

Dichotomous data are presented as percentages and continuous data are presented as the mean±SD. The prevalence of clinical, procedural and organizational variables between tested and non-tested patients was assessed with the Mann–Whitney two-independent-samples test.

Univariable and multivariable analyses were performed in order to examine the potential predictors of the execution of testing after PCI in the entire study population and, separately, in the subgroup of asymptomatic high-risk patients. Regression modelling was used to determine whether clinical, procedural and organizational variables were associated with the use of tests. The variables that defined the high-risk profile, such as diabetes, previous cardiac arrest, number of diseased vessels, left ventricular dysfunction, proximal left anterior descending PCI and PCI result were removed from covariates when the subset of asymptomatic high-risk patients was evaluated.

Difference in the frequencies of tested patients among symptomatic, high-risk and low-risk patients were evaluated with the chi-square test. All other statistical tests were 2-tailed. A *p* value <.05 was considered to be statistically significant. All analyses were performed with the use of the statistical program SPSS, version 15.

3. Results

A total of 473 patients were enrolled. Eight patients (1.7%) died during hospitalization and 45 patients were lost during follow-up. Therefore data from 420 patients (90%) were available for analysis.

During the 12-month follow-up a total of 425 FT and 39 planned CA were performed. Two hundred seventy-nine patients (66%) underwent at least one FT, and 33 of them underwent also one or more planned CA. Among patients who did not undergo any FT, CA was performed in 4 (1%) as a scheduled alternative follow-up procedure. Only 1 out of 3 patients with left main coronary artery PCI underwent planned CA after the procedure.

The total number of FT per patient ranged from 1 to 3, with 163 (58%), 86 (31%) and 30 (11%) patients having 1, 2 and 3 tests respectively. The timing of the first FT ranged from 0.2 to 11.5 months after PCI, with a median of

3.2 months. Second and third FT were performed at a median of 6.7 and 9.8 months after PCI, respectively.

Table 1 shows the characteristics of 137 patients who did not undergo any test and 283 patients who underwent at least one FT or planned CA. On average, as compared with patients who underwent at least one test, patients with no tests were older and were more likely to be women. They had a higher prevalence of diabetes mellitus, renal dysfunction, low ejection fraction and other concomitant vascular diseases. They also had a higher number of diseased coronary vessels, a higher prevalence of incomplete revascularization, a lower use of drug eluting stents, and they were more likely to have no reference center for post-PCI clinical follow-up. Noticeably, the occurrence of new symptoms during follow-up was not significantly different between patients with and without FT.

Table 1
Clinical, procedural and organizational characteristics of patients population.

	No tests (n=137)	≥1 tests (n=283)	p value
Demographics			
Age (y±SD)	69.4±10.7	63.2±9.6	0.000
Male sex %	73	83	0.016
Baseline clinical characteristics, %			
Diabetes	29.1	17.7	0.008
Previous stroke	6.6	2.8	0.111
Renal failure	16.8	8.5	0.011
Peripheral or carotid artery disease	13.1	6.7	0.030
Previous revascularization	37.2	32.5	0.339
Previous cardiac arrest	4.4	4.3	0.959
Number of diseased vessels	1.9±0.84	1.61±0.74	0.001
Left ventricular ejection fraction <40%	29.8	18.3	0.011
Clinical presentation, %			
Stable angina	39.4	39.6	0.975
Unstable angina	26.3	21.9	0.322
ST-elevation myocardial infarction	18.2	17	0.744
Non ST-elevation myocardial infarction	10.2	12.4	0.521
Silent ischemia	2.2	6	0.085
Other	3.6	3.2	0.802
Procedural characteristics, %			
Proximal LAD PCI	20.4	19.8	0.876
Multivessel PCI	21.5	15.8	0.154
PCI with drug eluting stents	34.6	46.2	0.025
PCI in restenotic lesions	11.7	11	0.825
Incomplete revascularization	44.6	31.9	0.013
Optimal PCI result	92	89.8	0.468
Follow-up location, %			
Same center that had performed PCI	39.3	44.9	0.308
Other clinical center	54.7	53.7	0.857
None	6	1.4	0.011
Occurrence of new symptoms after PCI, %			
Stable angina	10.2	16.6	0.082
Acute coronary syndromes	15.3	19.4	0.306

LAD: left anterior descending coronary artery; PCI: percutaneous coronary intervention.

A

Variable		R.R.	C.I.	P value
Age		0.94	0.92±0.96	<0.001
Male sex		1.81	1.11±2.95	0.017
Diabetes		0.52	0.32±0.85	0.008
Renal failure		0.46	0.25±0.85	0.013
Peripheral or carotid artery disease		0.48	0.24±0.94	0.032
Number of diseased vessels		0.63	0.48±0.81	<0.001
LVEF < 40%		0.53	0.32±0.87	0.012
PCI with DES		1.63	1.06±2.50	0.026
Incomplete revascularization		0.58	0.38±0.89	0.013
FU location: none		0.23	0.07±0.79	0.019
PCI at Center 5		1.82	1.00±3.32	0.049

B

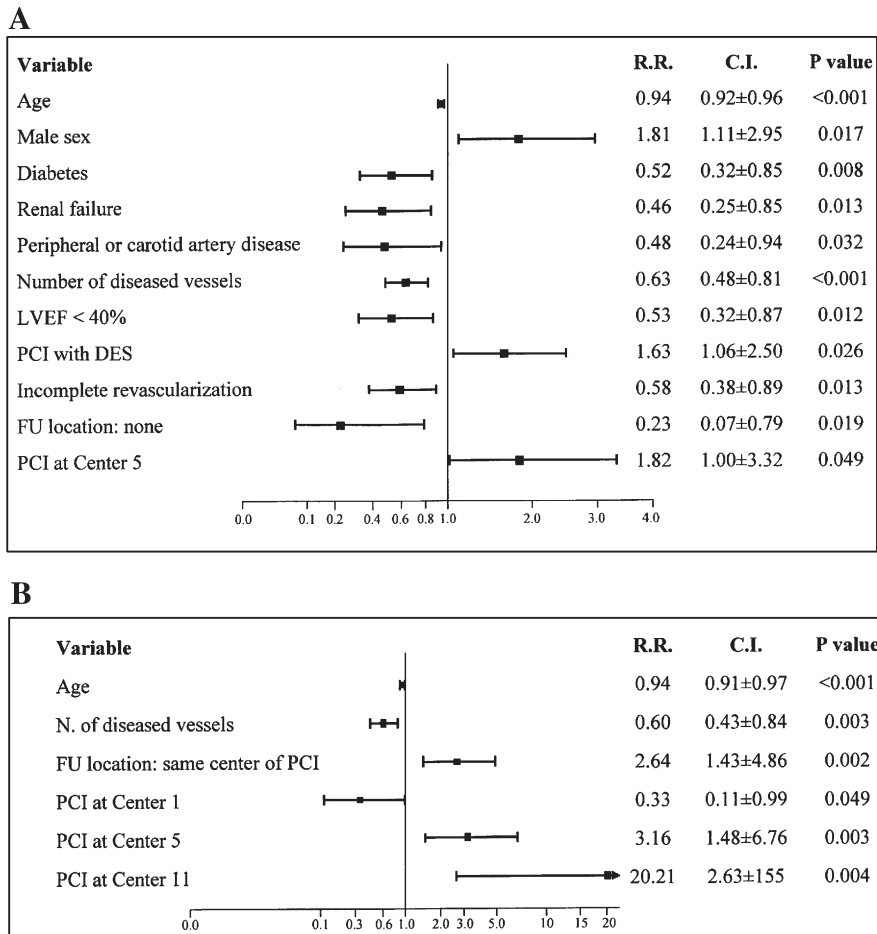| Variable		R.R.	C.I.	P value
Age		0.94	0.91±0.97	<0.001
N. of diseased vessels		0.60	0.43±0.84	0.003
FU location: same center of PCI		2.64	1.43±4.86	0.002
PCI at Center 1		0.33	0.11±0.99	0.049
PCI at Center 5		3.16	1.48±6.76	0.003
PCI at Center 11		20.21	2.63±155	0.004

Fig. 1. Clinical, procedural and organizational characteristics versus use of testing after PCI: univariable (Panel A) and multivariable (Panel B) analyses. LVEF: left ventricular ejection fraction, PCI: percutaneous coronary intervention, DES: drug eluting stent, FU: follow-up.

Univariable analyses identified a variety of clinical, procedural and organizational variables that were associated with the use of testing (Fig. 1A). However, multivariable analysis established that the variables with the largest influence on the odds of undergoing FT and planned CA after PCI were younger age, a lower number of diseased vessels, follow-up by the center that had performed PCI, and the specific center at which PCI was performed (Fig. 1B). Since data on left ventricular ejection fraction at the time of PCI were not available for 39 patients, multivariable analysis was repeated after removing ejection fraction from covariates, and the same results were obtained.

Acute coronary syndromes occurred in 27 patients (6.4%) and stable angina in 49 (11.6%) after PCI. Risk profile categorization of the residual 344 patients who remained asymptomatic resulted in 247 high-risk, 85 low-risk and 12 non classified patients (Fig. 2A).

During the study period at least one test was performed in 155 (63%) high-risk and in 64 (75%) low-risk patients (Fig. 2B). One-half of asymptomatic patients with FT had performed their first test and had completed their testing course within 3.2 and 5.9 months after PCI, respectively. Similarly, among asymptomatic patients that were scheduled for planned CA, one-half had undergone their procedure within 5.1 months after PCI.

Results of univariable analyses and multivariable regression model of the high-risk subgroup are shown in Fig. 3. Multivariable analysis demonstrated that, among high-risk asymptomatic patients, the only variables independently correlated with testing were age, renal failure, follow-up by the same center that had performed PCI, and to have undergone PCI in one of the participating centers.

4. Discussion

This multicenter study prospectively investigates the use of non-invasive testing and coronary angiography after PCI in a large cohort of consecutive patients enrolled in a short time in a representative region of an European country. We found that the use of FT and planned CA after PCI is unrelated to patient's symptoms, is not influenced by ACC/AHA guidelines and is not tailored to the risk period for restenosis.
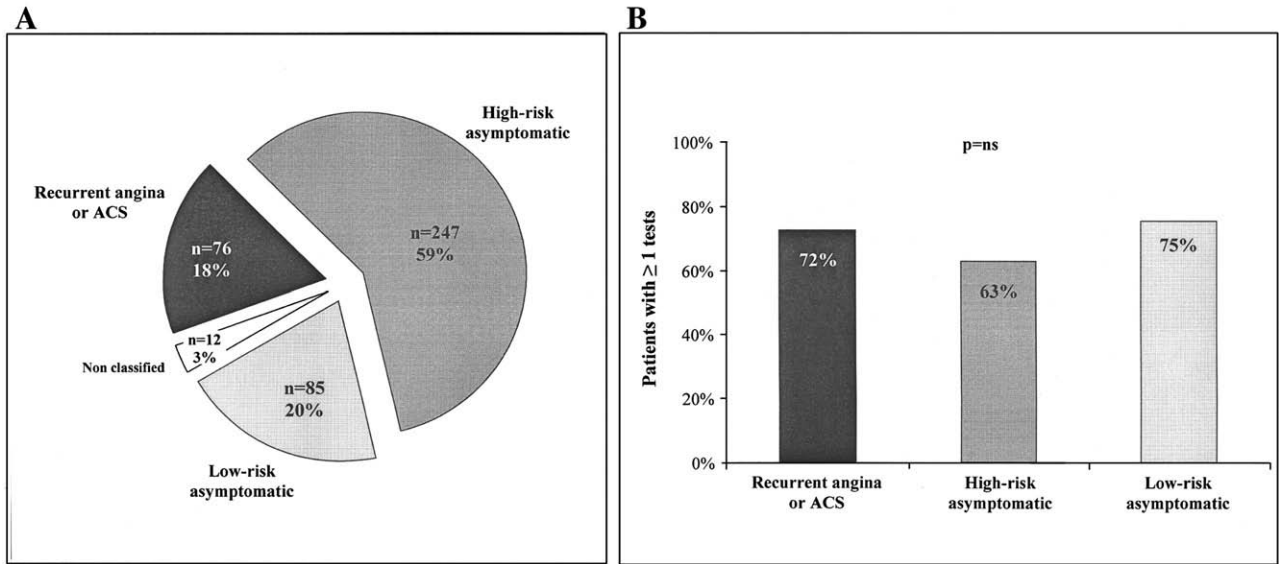
Fig. 2. Execution of testing in symptomatic and asymptomatic patients after PCI. Panel A: Stratification of the study population according to the occurrence of new symptoms and the risk profile. Panel B: Percentage of symptomatic, high-risk asymptomatic and low-risk asymptomatic patients undergoing testing over 12 months after PCI. ACS: acute coronary syndrome.

4.1. Patient's risk profile

Patients with no testing during a 12-month period after PCI had a higher average clinical, angiographic and procedural risk profile as compared with tested patients. Independently correlated with the use of functional and invasive testing were younger age and a lower number of diseased vessels. Of note,

clinical characteristics that are known to make the patient more likely to have restenosis and adverse events were not associated with a higher likelihood of undergoing FT or planned CA during follow-up. Conversely, our results emphasize the influence of organizational variables on the follow-up course. In fact, the propensity of the center that had performed PCI to test its own patients and the different standards of the centers at which
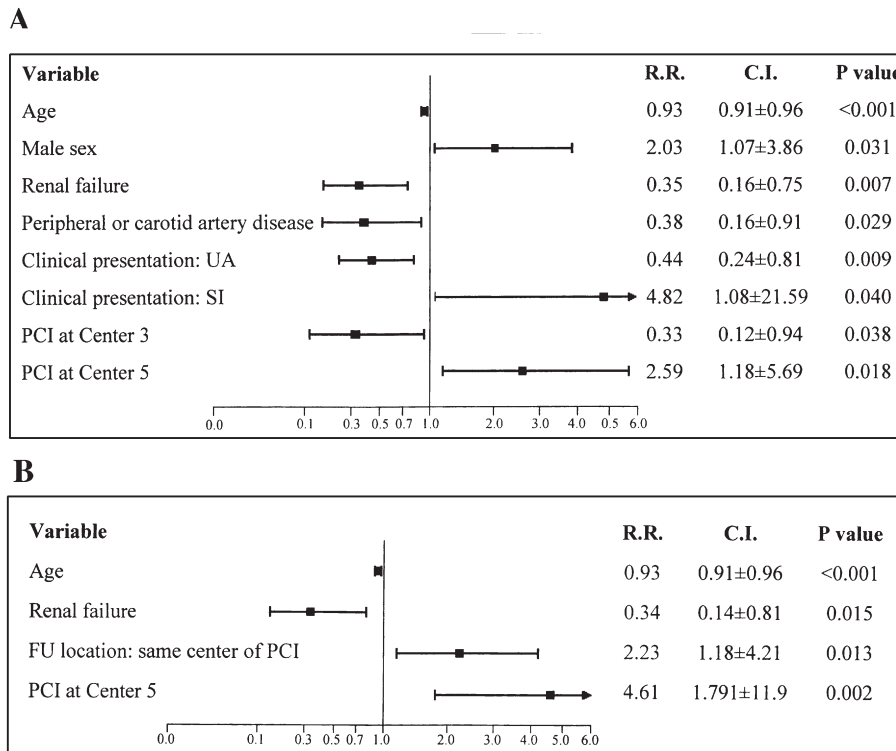

Fig. 3. Clinical, procedural and organizational characteristics versus use of testing after PCI among 247 high-risk asymptomatic patients: univariable (Panel A) and multivariable (Panel B) analyses. UA: unstable angina, SI: silent ischemia, PCI: percutaneous coronary intervention, FU: follow-up.

patients had the PCI, had a significant independent effect on the chance to undergo FT or CA after PCI.

Interpretation of the detrimental effect of age, greater extent of coronary artery disease and renal failure on the use of testing during follow-up is speculative. These variables may be deemed as indicators of a worse clinical status that could prevent patient's access to follow-up procedures. Moreover, clinicians may be unwilling to assess aggressively silent restenosis in these patients, limiting their strategy to surveillance of symptoms.

4.2. Impact of guidelines

ACC/AHA guidelines promote a selective use of FT according to symptoms and risk profile [5,7]. In our study 75% of low-risk patients underwent one or more tests, despite guidelines contraindication, and the percentage of tested patients was not significantly different among symptomatic, high-risk and low-risk patients. Furthermore, the occurrence of new symptoms, which is the only class I indication for post-PCI FT [7], showed no correlation with the execution of tests at both univariable and multivariable analysis. The routine use of FT for the assessment of asymptomatic ischemia after PCI is still a matter of debate. The prognostic importance of asymptomatic restenosis is not well established [10–16], although severity and extent of myocardial ischemia, whether painful or silent, is highly predictive of future cardiovascular events [11]. PCI is generally indicated in patients with silent ischemia and a moderate to large area of jeopardized myocardium, and repeat PCI is a reasonable treatment for patients who develop in-stent restenosis [5]. ACC/AHA guidelines give controversial recommendation (Class II B) for the use of FT after PCI in high-risk asymptomatic patients [7]. This class of indication probably reflects not only uncertainty on the benefit of treatment of clinically silent restenosis, but also the low sensitivity of exercise ECG for the prediction of restenosis [6,10,14]. In recent years the subgroup of asymptomatic patients with high-risk features after PCI has probably increased because of the widespread use of drug eluting stents [9], which have been shown to be effective in more complex clinical and procedural settings [17,18]. In fact, patients with high-risk characteristics who remained asymptomatic after PCI were up to 65% of our overall population. Thus, our results emphasize that indication for FT is substantially undefined for the majority of patients undergoing PCI in the current clinical practice. In this subgroup as well we found that the use of follow-up tests depended on age and the different standards of the centers rather than the clinical and procedural profile of the patient.

4.3. Test timing

The restenotic process occurs over the first 8 months after PCI and most patients develop restenosis-related symptoms during a similar time frame [19]. Furthermore, the risk period for restenosis could be prolonged with the use of drug eluting stents [20,21]. Despite that, in asymptomatic patients we found a wide variation in the timing within which the FT and even the planned CA were done. Most patients underwent their first FT very early and, more importantly, completed their follow-up course and underwent planned CA prematurely with respect to the end of the risk period for restenosis.

4.4. Previous studies

To our knowledge the ROSETTA registry [8] is the only previously published prospective study that evaluated the use of FT after PCI in clinical practice. The authors categorized the patterns of use of FT in a multicenter extraEuropean setting as "routine" and clinically-driven "selective" strategy. Although patients with no FT were included in the group of selective strategy together with patients with clinically-driven FT, they found that 61% of patients had routine functional testing and that the strategies varied widely among centers. When they compared patients with and without FT, younger age, male sex and the location of the center at which the patient had the PCI were found as the only independent determinants of the use of FT. Consistency between observations from ROSETTA registry and our study suggest that these results can be generalized to different geographic areas, and that the first observations obtained in a pre-drug eluting stent population can be extended to the contemporary clinical setting.

4.5. Limitations

Some potential limitations of our study should be noted.

First, identification of patients with II B class of indication for FT is somewhat arbitrary, since ACC/AHA guidelines list a non-conclusive number of features for this subgroup. For example, renal failure or troponine and creatine kinase-MB elevation, which are associated with an increased risk for adverse events after PCI [22,23], are not mentioned and were not taken into account for definition of the high-risk subgroup in our analysis. As a result, patients with a real high-risk for restenosis and clinical events after PCI could be potentially underestimated.

Second, lack of data on left ventricular ejection fraction in 39 patients may translate into a subsequent reduction of analyzable patients on multivariable analysis. However, when we repeated the same analysis after removing ejection fraction from covariates we obtained the same results, which corroborated the reliability of our conclusions.

Finally, some patients may undergo FT for reasons other than assessment of restenosis. Particularly, patients with acute myocardial infarction or left ventricular dysfunction may be tested to determine functional status after hospital discharge. However, none of the variables that are potentially related to such a use of FT had a significantly higher prevalence in patients with tests and none had a correlation with the use of tests in the univariable and multivariable analyses.

5. Conclusions

The use of functional and invasive testing after PCI in the "real world" is unrelated to clinical and procedural characteristics of the patients, and depends on patient's age and logistics, such as the different standards of the clinical centers performing PCI and the reference center for follow-up. The timing of post-PCI FT and planned CA varies widely, and is not tailored to the risk period for restenosis. ACC/AHA guidelines, that favor a selective use of testing according to the occurrence of new symptoms and the risk profile of the patient, have no impact on clinical practice. However, the indication of guidelines is controversial (Class II B) for the majority of patients undergoing PCI in the current clinical setting, which are patients with high-risk features for restenosis who remain asymptomatic after PCI.

These results emphasize the need for further research on the indication and benefit of FT following PCI.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [24].

Appendix A. The AFTER investigators

C. Pristipino, V. Pasceri, G. Speciale, San Filippo Neri Hospital, Rome, Italy; F. Burzotta, F. Giannico, Catholic University, Rome, Italy; R. Serdoz, F. Monti, San Pietro Hospital, Rome, Italy; A. Berni, S. Abbolito, R. Coluccia, S. Andrea Hospital, Rome, Italy; G. Sardella, R. Colantonio, G. Conti, Policlinico Umberto I, Rome, Italy; A. Danesi, A. Ferraironi, R. Ricci, Santo Spirito Hospital, Rome, Italy; G. Di Sciascio, G. Patti, Campus Biomedico University, Rome, Italy; P. Mazzarotto, F. Gemelli, P. Stecconi, San Carlo Hospital, Rome, Italy; L.D. Zingales, D. Irini, D. Cesari, Belcolle Hospital, Viterbo, Italy; P. Loschiavo, S. Rigattieri, Sandro Pertini Hospital, Rome, Italy; A. Sciahbasi, E. Lioy, Policlinico Casilino, Rome, Italy; G. Gioffrè, A. Gaspardone, Sant'Eugenio Hospital, Rome, Italy.

References

[1] Patterson RE, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. Circulation 1995;91:54–65.

[2] Shaw LJ, Marwick TH, Berman DS, et al. Incremental cost-effectiveness of exercise echocardiography vs. SPECT imaging for the evaluation of stable chest pain. Eur Heart J 2006;27:2448–58.

[3] Saririan M, Cugno S, Blankenship J, et al. Routine versus selective functional testing after percutaneous coronary intervention in patients with diabetes mellitus. J Invasive Cardiol 2005;17:25–9.

[4] Pinto DS, Stone GW, Ellis SG, et al. Impact of routine angiographic follow-up on the clinical benefits of paclitaxel-eluting stents. results from the Taxus-IV trial. J Am Coll Cardiol 2006;48:32–6.

[5] Smith Jr SC, Feldman TE, Hirshfeld Jr JW, et al. ACC/AHA/SCAI 2005 Guideline update for percutaneous coronary intervention—full text: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. 2006. www.cardiosource.com/guidelines/guidelines/percutaneous/perc_PDF.pdf (accessed 19 Oct 2007).

[6] Klocke FJ, Baird MG, Bateman TM, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. 2003. www.americanheart.org/downloadable/heart/1061222494555RNIFullTextFinal.pdf (accessed 19 Oct 2007).

[7] Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. 2002. www.americanheart.org/downloadable/heart/1032279013658exercise.pdf. (accessed 19 Oct 2007).

[8] Eisenberg MJ, Schechter D, Lefkovits J, et al. Use of routine functional testing after percutaneous transluminal coronary angioplasty: results from the ROSETTA Registry. Am Heart J 2001;141:837–46.

[9] Lucas FL, DeLorenzo MA, Siewers AE, et al. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993–2001. Circulation 2006;113:374–9.

[10] Desmet W, De Scheerder I, Piessens J. Limited value of exercise testing in the detection of silent restenosis after successful coronary angioplasty. Am Heart J 1995;129:452–9.

[11] Cohn PF, Fox KM. Silent myocardial ischemia. Circulation 2003;108:1263–77.

[12] Stern S. Angina pectoris without chest pain. Clinical implications of silent ischemia. Circulation 2002;106:1906–8.

[13] Zellweger MJ, Weinbacher M, Zutter AW, et al. Long-term outcome of patients with silent versus symptomatic ischemia six months after percutaneous coronary intervention and stenting. J Am Coll Cardiol 2003;42:33–40.

[14] Hecht HS, Shaw RE, Chin HL, et al. Silent ischemia after coronary angioplasty: evaluation of restenosis and extent of ischemia in asymptomatic patients by tomographic thallium-201 exercise imaging and comparison with symptomatic patients. J Am Coll Cardiol 1991;17:670–7.

[15] Davies RF, Goldberg AD, Forman S, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study two-year follow-up: outcomes of patients randomized to initial strategies of medical therapy versus revascularization. Circulation 1997;95:2037–43.

[16] Erne P, Schoenenberger AW, Burckhardt D, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: the SWISSI II randomized controlled trial. JAMA 2007;297:1985–91.

[17] Eisenberg MJ, Konnyu KJ. Review of randomized clinical trials of drug-eluting stents for the prevention of in-stent restenosis. Am J Cardiol 2006;98:375–82.

[18] Klein LW. Are drug-eluting stents the preferred treatment for multivessel coronary artery disease. J Am Coll Cardiol 2006;47:205–7.

[19] Serruys PW, Luijten HE, Beatt KJ, et al. Incidence of restenosis after successful coronary angioplasty: a time-related phenomenon. A quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months. Circulation 1988;77:361–71.

[20] Park DW, Hong MK, Mintz GS, et al. Two-year follow-up of the quantitative angiographic and volumetric intravascular ultrasound analysis after nonpolymeric paclitaxel-eluting stent implantation: late "catch-up" phenomenon from ASPECT Study. J Am Coll Cardiol 2006;48:2432–9.

[21] Valgimigli M, Malagutti P, van Mieghem CA, et al. Persistence of neointimal growth 12 months after intervention and occurrence of delayed restenosis in patients with left main coronary artery disease treated with drug-eluting stents. J Am Coll Cardiol 2006;47:1491–4.

[22] Best PJ, Lennon R, Ting HH, et al. The impact of renal insufficiency on clinical outcomes in patients undergoing percutaneous coronary interventions. J Am Coll Cardiol 2002;39:1113–9.

[23] Kini AS, Lee P, Marmur JD, et al. Correlation of postpercutaneous coronary intervention creatine kinase-MB and troponin I elevation in predicting mid-term mortality. Am J Cardiol 2004;93:18–23.

[24] Coats AJ. Ethical authorship and publishing. Int J Cardiol 2009;131:149–50.