Follow-up of patients undergoing percutaneous coronary intervention

Alfredo R. Galassi, Corrado Tamburino

Clinical Division of Cardiology, Department of Internal Medicine and Systemic Disease, Ferrarotto Hospital, University of Catania, Catania, Italy

Key words:
Coronary angiography; Coronary angioplasty; Percutaneous coronary intervention; Stress echocardiography; Stress testing.

Percutaneous coronary intervention (PCI) has become a mainstay in the treatment of patients with coronary artery disease in recent years. Although increasingly complex lesions and higher-risk patients are being successfully treated, restenosis, incomplete revascularization and progression of disease continue to cause a need for a clinical functional assessment, in order to reduce morbidity.

Angiographic systematic follow-up, although traditionally considered the gold standard for restenosis and disease progression, should nowadays be considered a valuable approach only to monitor small groups of very high-risk patients. Recurrence of symptoms itself has low sensitivity and specificity in detecting restenosis and myocardial ischemia. Exercise testing may provide useful information on symptoms and functional capacity of the patient; however, it has a low diagnostic power for restenosis and myocardial ischemia with a low sensitivity and specificity. Conversely, the significantly increased sensitivity and specificity obtained by stress nuclear or echocardiographic imaging provide great advantage for the clinical assessment of these patients. Additional advantages of stress imaging are the ability to assess location and extent of myocardial ischemia regardless of symptoms as well as to evaluate patients who are unable to exercise or who have an uninterpretable electrocardiogram. Furthermore, the clear superiority of stress imaging with regard to specificity and predictive value for post-revascularization events makes this functional approach of paramount importance for assessing prognosis of such patients. However, as predictive values of functional stress tests are highly dependent on the pre-test probability of disease, follow-up following PCI should always take into consideration the clinical characteristics of the patient (such as diabetes and age), the angiographic characteristics (severity of disease, myocardium at risk, left ventricular function), the procedural characteristics (length of the lesion, vessel size, number of stents implanted, etc.), symptoms and physical activity of the patient. All these parameters together will assess the risk of the patient and will help to choose a functional appropriate follow-up protocol.

(Ital Heart J 2005; 6 (6): 530-539)

Address:
Dr. Alfredo R. Galassi
Via Antonello da Messina, 75
95021 Acicastello (CT)
E-mail:
argalassi@virgilio.it

Introduction

Since 1977, when Gruentzig et al.[1] introduced percutaneous transluminal coronary angioplasty (PTCA), percutaneous coronary intervention (PCI) has exponentially grown, especially in recent years; this is mainly due to low procedural risk, greater operator experience and therapeutic efficacy which in turn has determined widespread application of the procedure from chronic stable angina to acute coronary syndromes, from single vessel disease to multivessel disease. Furthermore, procedural technological improvement mainly due to stent implantations and more recently to drug-eluting stent use has provided improved results in complex lesions, small-diameter vessels, chronic total occlusions, and diseased bypass conduits. Nowadays, for many patients with multivessel disease, PCI is a real alternative to coronary artery bypass graft (CABG)[2] and the number of PCI is likely to increase further as population age increases and as many complex cases are treated with PCI rather than surgery. Therefore, the optimal management of patients treated with PCI is challenging: not only the clinical benefit of patients should be considered but also the cost-efficacy ratio of both procedures and follow-up.

Restenosis, incomplete revascularization and disease progression

Restenosis. Coronary restenosis is defined as the "Achilles heel" of PCI occurring in 15-50% of patients after an initial successful PTCA[3-6]. The introduction of coronary artery stenting had reduced the rate of restenosis to < 20%[7] and adjunctive therapy for stenting, such as brachytherapy and namely drug-coated stents, has shown to further decrease restenosis rate significant-

ly[8,9]. The occurrence of restenosis is of prognostic importance as, in the majority of cases, it causes myocardial ischemia which in turn with diabetes is considered the most powerful predictor of cardiac events at long-term follow-up after PCI[10]. When restenosis does occur, patients generally present angina within 3 to 9 months of the procedure and usually after a symptom-free period[11,12]. Angina developing after 9 months is usually due to disease progression[13]. However, it has been reported that up to 40% of patients developing angina after PCI do not have significant angiographic restenosis and on the other hand that 18 to 58% of patients with restenosis remain asymptomatic (Table I)[11,12,14-18]. Although some earlier studies[16,19] appeared to demonstrate a favorable prognosis for patients with asymptomatic restenosis, more recent works confirmed such patients to be at increased risk for adverse events[10,20,21]. In one of these studies Zellweger et al.[10] prospectively followed for 4 years 356 patients who underwent coronary stenting and routine single-photon emission computed tomography (SPECT) imaging 6 months thereafter; they found that the extension and severity of ischemia determined by myocardial perfusion imaging (MPI) and not symptom status, were the best predictors of outcome. This study also confirmed the findings of Hernandez et al.[16] who followed 839 patients undergoing ECG stress testing and angiography control at 6 to 9 months and who concluded that asymptomatic restenosis is a frequent phenomenon with a good prognosis mainly in patients with a negative exercise test result. Thus, all these studies highlight the importance of silent ischemia, assessed by nuclear imaging, in improving the long-term outcome of this growing patient population.

Incomplete revascularization. Complete revascularization remains a desirable goal, and a satisfactory outcome may be obtained with functionally complete revascularization with PTCA or CABG[22,23]. However, complete revascularization may not be possible or not easy to plan in many patients. Thus, revascularization of the culprit lesion may be part of an incomplete revascularization strategy which may be of value and a common clinical practice in many cases. Clinical reasons include, among others, unstable angina, recent myocardial infarction, severe left ventricular dysfunction, urgent/emergent PCI, preexisting renal failure for which the amount of angiographic contrast media should be limited, premature termination of the procedure for unexpected problems, such as in elderly or frail patients who cannot lay flat for prolonged periods[24]. In other cases, complete revascularization is not possible because of chronic total occlusions, adverse stenosis morphology, or simply not planned in the presence of less than severe (> 50% but < 70%) coronary narrowing. In the BARI trial comparing CABG with multivessel PCI, the 5-year survival did not differ between the two treatments despite the fact that 91% of significant lesions were bypassed in the CABG patients compared to 54% of significant lesions in the PTCA patients[22]. In the same trial, cardiac death, repeat revascularization and angina at 5-year follow-up were similar in patients in whom a PTCA was performed as a planned incomplete revascularization, as compared to those with a planned complete revascularization. Furthermore, even in patients for whom complete revascularization with PTCA was planned, only 50% of lesions were both attempted and dilated. Similar results were obtained by Vandormael et al.[25] who found an important symptomatic relief achieved with partial revascularization in patients with multivessel disease. In these patients the 1-year cardiac event rate was not significantly higher than the rate in the group with complete revascularization. At follow-up 66% of patients with complete revascularization were asymptomatic and 84% had clinical improvement; this was similar to 58 and 85%, respectively for patients with incomplete revascularization. Thus, incomplete revascularization seems to be a valuable solution when a culprit lesion can be identified, particularly when this vessel is a favorable lesion which serves a large non-infarct territory, or in case of an acute coronary syndrome where there is the need for stabilizing the patient's conditions[26,27].

Table I. Chest pain as a marker of restenosis after percutaneous coronary intervention.

Author	Year	No. patients	Follow-up angiography (months)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Holmes et al.[14]	1984	524	6	79	68	56	86	72
Nobuyoshi et al.[12]*	1988	229	6-12	41	95	91	59	66
Hecht et al.[15]	1991	116	6	64	34	59	39	52
Hernandez et al.[16]**	1992	839	6-9	52	NA	NA	NA	NA
Legrand et al.[17]	1997	325	6	56	86	51	89	80
Ruygrok et al.[11]	2001	2690	6	45	NA	NA	NA	NA
Overall performance				51§	75§	62§	77§	71§

Data reflect 6-month symptom status and angiographic findings, unless otherwise indicated. NA = not available; NPV = negative predictive value; PPV = positive predictive value. * 1-year data; ** 6 to 9-month data; § weighted average. From Giedd and Bergmann[18], with permission from the American College of Cardiology Foundation.

Progression of disease. Progression of disease in untreated vessel segments remains an important problem in patients with coronary artery disease following any type of revascularization, occurring at rates approaching 7% per year in both symptomatic and asymptomatic patients[28]. More than one-half of patients with angina ≥ 1 year after PCI have a new obstructive lesion or significant worsening of a previously nonobstructive stenosis[29]. Similarly, in another angiographic study of patients presenting with angina > 1 year after PCI, significant disease progression was found in 57% of cases[30]. More recently Alderman et al.[31] reported data from a 5-year angiographic follow-up of a subgroup of patients in the BARI trial and found that native coronary disease progression occurred more often than failed revascularization in both PCI- and CABG-treated patients as a cause of jeopardized myocardium and angina recurrence. These findings underline how in a relatively short timeframe coronary disease progression may indeed be a reality which should be monitored carefully at follow-up.

Invasive follow-up

Angiographic assessment is traditionally considered to be the gold standard for the diagnosis of restenosis; it is also considered to be necessary to confirm the suspicion of restenosis based on clinical and non-invasive grounds. Systematic angiographic control after PCI has been considered in the past a valuable approach to monitor patients. Weintraub et al.[32] compared the outcome of 3363 patients who were evaluated systematically by coronary angiography with those of 3858 patients followed clinically. Although, as expected, the rate of revascularization was higher among patients followed by angiography, this latter group had also a better survival rate at 6-year follow-up than patients followed clinically. Similar results were obtained by other authors in a registry of 400 patients followed over 10 years; mortality was 2.7 times higher in those patients who did not undergo angiographic follow-up as compared to those who were re-evaluated systematically invasively[33]. Despite the methodological limits inherent to registry studies, the lack of patient randomization and of stent use in these two studies, the favorable results on survival obtained with the invasive approach should not be underestimated. Bearing all that in mind, the systematic angiographic control may be difficult to apply when considering the related limits of this approach due to logistic reasons, high cost-efficacy ratio and associated unjustified risk of morbidity and mortality which albeit small should be taken into consideration[34,35]. Furthermore, intermediate lesions, as those assessed between 50-70% and recognized by angiography as "restenosis" have a favorable prognosis under medical treatment without revascularization[36,37]. Indeed, invasive evaluation by coronary Doppler or pressure wire[38-40] or non-invasive evaluation by imaging technique such as myocardial scintigraphy[41,42] or stress echocardiography[43], would allow a more accurate evaluation of the functional significance of the lesion in the follow-up of these patients, and prevent an excess of revascularization caused by the "oculostenotic reflex". Finally, in case of restenosis the temporal occurrence of the phenomenon should be taken into account. The phenomenon of restenosis reaches the peak around 4-5 months to diminish thereafter over 3 years[44,45]. This may justify an attitude of "watchful waiting" in the case of intermediate restenosis found at angiography around this period after PCI. This is further reinforced by the fact that patients with angiographic restenosis who remain asymptomatic and who have no evidence of exercise-induced ischemia have a benign outcome[19]. This is why in routine clinical practice, as well as in clinical trials, both clinical outcome and event free survival of the patient (that is without death, Q wave or non-Q wave myocardial infarction, or the need for target vessel revascularization) have been considered more important than angiographic restenosis. Thus, in recent years a consensus has progressively appeared regarding the follow-up strategy and the indications for target vessel revascularization, no longer based on the angiographic 6-month control, but rather only on symptoms and non-invasive detection of ischemia, considered the "angioplastically correct" follow-up strategy as defined by Schiele[46]. Nowadays a systematic angiographic control after PCI may be considered a valuable approach only to monitor small groups of patients, such as those who apply to clinical trials whose endpoint is restenosis, those at very high risk who implant a drug-eluting stent in a left main stenosis or in a bifurcation lesions, and those who perform complicated PCI procedures whose long-term results are unknown such as brachytherapy, or drug-eluting stent implantation for aggressive in-stent restenosis[47]. It is important to note that, in case of procedures which delay re-endothelialization such as brachytherapy or drug-eluting stent implantation, systematic angiographic control should be delayed up to 8 months.

Predictive value of symptom recurrence

Although in patients with single-vessel disease and no stent implantation, symptom recurrence is often associated with restenosis, in others despite recurrent symptoms the previously dilated artery is widely patent without significant restenosis. The problem is even more difficult in patients who have multivessel disease in whom continued or recurrent symptoms may be related to undilated stenoses, progression of disease in other vessels, or long-term endothelial dysfunction after coronary artery stenting with consequent intense coronary vasoreactivity[48]. Indeed, several investigators have shown that recurrence of symptoms alone has a

low sensitivity and specificity for the detection of restenosis and myocardial ischemia following PCI (Table I)[11,12,14-18]. Furthermore, angina occurring post-PCI is not a frequent occurrence, accounting approximately for only 20% of cases[10]; thus, restenosis is clinically silent in nearly 60% of patients following PTCA[12] or stenting[11]. Importantly, the presence of angina before PCI does not imply that restenosis is associated with symptoms as the great majority of patients who present silent ischemia after PCI had angina before the procedure[14].

Use of non-invasive testing

Due to the recognized limited accuracy of clinical symptoms to follow patients after PCI, the use of non-invasive testing such as exercise testing, myocardial scintigraphy and stress echocardiography is generally employed in the management of these patients.

Exercise testing. Exercise testing is a widely used method particularly valuable in assessing cardiovascular status after the occurrence of a cardiac event or therapeutic interventions such as PCI. It may provide useful information on symptoms and functional capacity of the patient. When performed after discharge it is helpful for activity counseling and/or exercise training as part of cardiac rehabilitation programs[49]. However, data obtained from two recent meta-analyses demonstrate that exercise testing, even if information from the ECG and symptomatic data are synthesized, has a low diagnostic power for restenosis and myocardial ischemia with a sensitivity of 46% and a specificity of 77%[50,51]. The use of stress nuclear imaging increases significantly the sensitivity to 87% and the specificity to 78% while that of stress echocardiography imaging increases the sensitivity to 63% and the specificity to 87% (Fig. 1)[50,51]. The lower sensitivity of exercise ECG compared to imaging techniques in clinical practice may worsen further, by inadequate stress yielding low exercise heart rates, the presence of drugs that are known to influence test results and the extent of disease in vessels other than those dilated. Furthermore, exercise ECG does not permit the determination of location of ischemia, nor does it accurately assess the extent of ischemia; these factors are often crucial in the clinical decision-making post-PCI.

Stress imaging. Although exercise testing has the advantage of widespread availability and relatively low cost, the higher test accuracy obtained by stress imaging provides great advantages for the clinical assessment of these patients. An additional advantage is that pharmacological imaging stress testing may be performed in patients who are unable to exercise or who have an uninterpretable ECG.

Several studies[15,52-58] employing SPECT-MPI at varying times from PCI have shown high levels of sensitivity and specificity of nuclear imaging when compared to those of coronary angiography (Table II). The overall performance of SPECT-MPI in detecting myocardial ischemia was 79% for both sensitivity and specificity. These values improve when myocardial scintigraphy is performed > 2 months from revascularization. The decreased specificity observed when MPI is performed early after PCI was initially noted following PTCA[59-61] and more recently after coronary stenting[62,63]. Indeed, myocardial perfusion may be altered as a consequence of impaired flow reserve due to an epicardial coronary stenosis or in the absence of coronary obstruction as a consequence of an endothelial dysfunction and medial injury at the treated site or abnormal microvascular and resistive vessel function distal to the PCI site as shown by various authors[64,65].

Similar to MPI, echocardiography in conjunction with exercise provides a useful functional assessment of coronary lesions and has a high concordance with myocardial scintigraphy[66]. Mertes et al.[67] found that exercise echocardiography may predict the development of recurrent ischemia after PTCA, with a sensitivity of 83% and a specificity of 85%. The functional significance of a lesion may also be determined with the use of pharmacological stress[68]. For the detection of coronary restenosis, exercise[69], dipyridamole[70], and dobutamine echocardiography[71] have

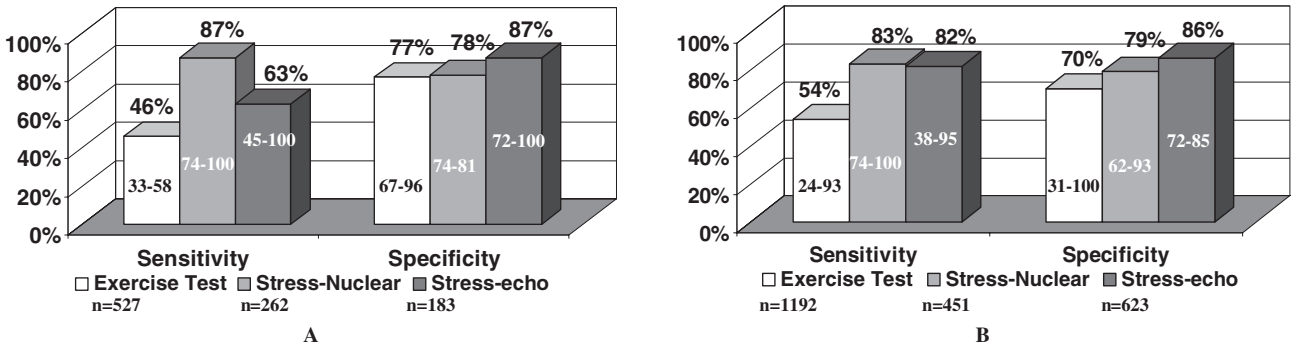

Figure 1. *Sensitivity and specificity of functional testing for the detection of restenosis (> 50% stenosis) after percutaneous coronary intervention: data from the meta-analyses of Garzon and Eisenberg[50]* (A) *and Dori et al.[51]* (B).

Table II. Accuracy of myocardial single-photon emission computed tomography (SPECT) imaging after percutaneous coronary intervention (PCI).

Author	Year	No. patients	PCI modality	Patients with angina (%)	Mean time to SPECT (months)	Mean time to angiography	Sensitivity (%)	Specificity (%)	Accuracy (%)
Hecht et al.[15]	1991	116 41§ 75§§	PTCA	65 0 100	6 months	1 week	93 96§ 91§§	77 75§ 77§§	86 88§ 85§§
Marie et al.[52]	1993	62§	PTCA	0	6 months	3 days	94§	84§	87§
Milan et al.[53]*	1996	37 20°	PTCA	NA	"Late"	1 month	88 92°	78 67°	83 NA
Kosa et al.[54]	1998	82 (99) 35 (52)°	Stenting	NA NA	7 months	1 month	79 100°	78 82°	79 85°
Milavetz et al.[55]	1998	33	Stenting	64	3 months	5 days	71^ 95^^	– 73^^	67^ 88^^
Caner et al.[56]**	1998	34 (37)	PTCA	NA	2-48 months	1 month	76	79	78
Beygui et al.[57]	2000	179 (208)§ 111 (138)	PTCA	0	6 months	7 days	63§ 56°	77§ 81°	71§ 74^^
Galassi et al.[58]	2000	97 (107) 46 (56)°	Stenting	NA	4 months	2 months	82# 76°	84# 95°	83# 89°
Overall performance							79##	79##	79##

Number of treated territories is indicated in parentheses; restenosis is defined as ≥ 50% diameter stenosis unless otherwise indicated. NA = not available; PTCA = percutaneous transluminal coronary angioplasty. * all patients referred because of "equivocal" exercise stress tests, values reported are for qualitative analyses; ** dobutamine stress used for all patients; § patients with "silent" ischemia; §§ patients with "symptomatic" ischemia; ° patients without prior infarction; ^ calculations using ≥ 50% cross-sectional area narrowing definition; ^^ calculations using ≥ 70% cross-sectional area narrowing definition; # calculations based upon vascular territories; ## weighted average. From Giedd and Bergmann[18], with permission from the American College of Cardiology Foundation.

shown a diagnostic accuracy similar to that seen with myocardial scintigraphy although a lower sensitivity (75 to 87%) and a slightly higher specificity (84 to 95%) was found in the direct comparison with nuclear data[69,70].

Prognostic value of stress imaging following percutaneous coronary intervention. Both perfusion imaging and stress echocardiography have a clear superiority with regard to specificity and predictive value in post-revascularization events[72-75]. Indeed, for nuclear imaging, these findings have been shown regardless of the method selected and include the use of ^{201}Tl or ^{99m}Tc radiopharmaceuticals or after varying modes of stress imaging[60,76-78]. In the Angioplasty Compared to Medicine Study, 328 patients were randomized to PTCA or medical therapy. At 6 months after randomization 82% of patients underwent stress MPI and were followed for > 5 years. Mortality in the PTCA group was 20% for those with a reversible defect vs 7% for those without such a defect (p = 0.03). On multivariate analysis, the strongest predictors of mortality were diabetes, smoking, and a reversible perfusion defect at myocardial scintigraphy[77]. Similarly, the relative prognostic information derived from myocardial SPECT scintigraphy at 1 year after revascularization in patients with multivessel coronary artery disease included in the prospective EAST trial reveals a strong relation between detected ischemia on thallium scintigraphy and subsequent events[76]. More recently, in patients with incomplete revascularization procedures we demonstrated that exercise myocardial scintigraphy provides significant independent information concerning the subsequent risk of both hard and soft cardiac events, with a composite annualized event rate < 2% for patients with a normal scan (Fig. 2)[79]. Myocardial scintigraphy is able to provide incremental prognostic information after adjusting for clinical, angiographic and exercise variables and to predict the occurrence of cardiac hard and soft events when separating patients according to the presence of myocardial ischemia and necrosis. The results of this study and of a subsequent one of our group suggest that certain high-risk patients, such as those with multivessel coronary artery disease, treated by incomplete revascularization may benefit from routine nuclear testing[79,80]. This concept seems to be true also for low-risk patients as shown by Ho et al.[81] who studied 211 patients between 1 and 3 years after PCI and monitored them for 7.3 years. Despite a low overall annual event rate of 1%, an abnormal scintigraphy was significantly predictive of cardiac death or myocardial infarction, whereas a normal myocardial scan was associated with low risk.

Influence on the diagnostic capability of functional testing. Because of the increasing use during PCI of coronary stenting and the consequent reduced rate of

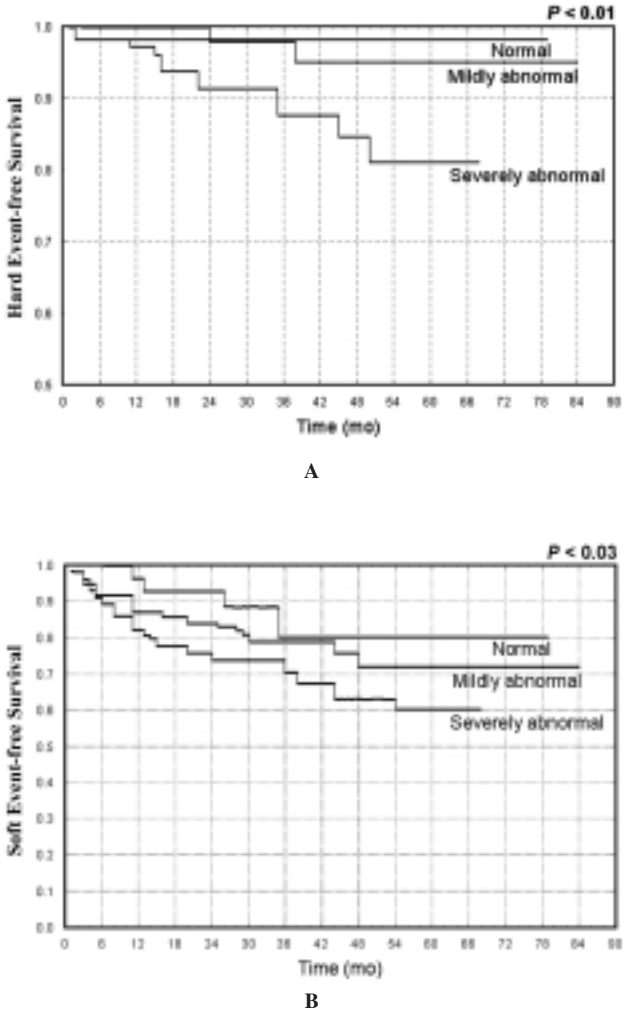

Figure 2. *Cardiac hard* (A) *and soft* (B) *event-free survival in patients with normal, mildly abnormal or severely abnormal single-photon emission computed tomography ^{99m}Tc-tetrofosmin scintigraphy.*

restenosis the diagnostic ability of stress imaging is declining substantially. It is important to note that patients with a low pre-test probability of restenosis, paucity of symptoms, reduced severity of underlying coronary artery disease and number of risk factors would have a high negative predictive value with either exercise testing, or myocardial scintigraphy and stress echocardiography (Fig. 3)[50]. Therefore, a negative exercise test result may be clinically useful (e.g., clearing a patient for activity) in patients with a low pre-test probability of disease, indicating in such patients a good prognosis. However, as the risks of exercise testing in these patients are extremely low, the main arguments for not performing an exercise test are that the information provided would not justify the extra costs of obtaining that information (i.e. the test would not be cost-effective in that given situation) and/or the test might provide misleading information that could lead to inappropriate or unnecessary additional testing or therapy (both of which may have higher risks than exercise testing)[49]. On the other hand, stress imaging would be bet-

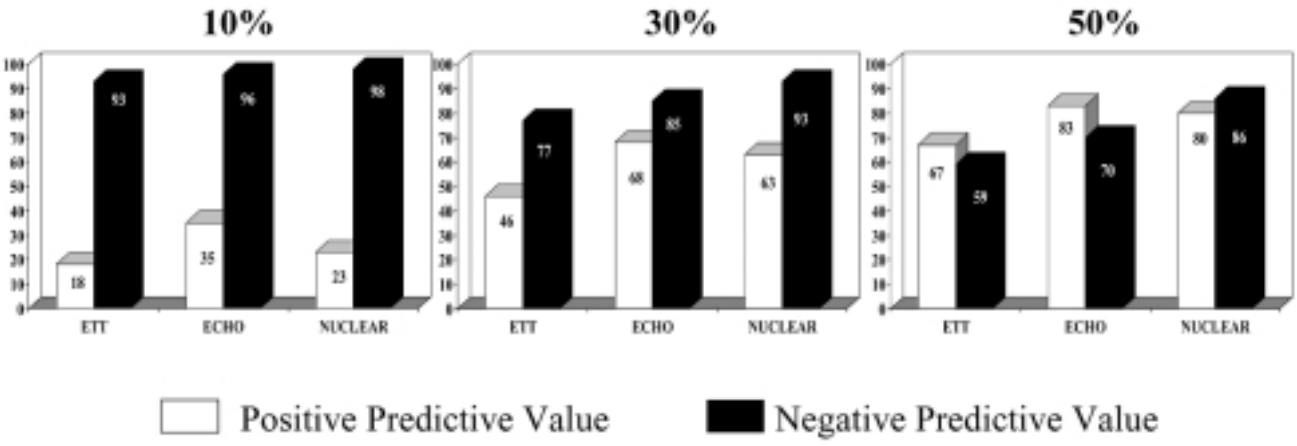

Figure 3. *Negative and positive predictive values of exercise treadmill testing (ETT), stress echocardiography and stress nuclear imaging in patients with low (10%), medium (30%) and high (50%) pre-test probability of restenosis after percutaneous coronary intervention. From Garzon and Eisenberg[50], modified.*

ter for patients with a medium to high pre-test probability of restenosis[82] (Fig. 3). Indeed, in these patients myocardial ischemia whether symptomatic or silent worsens prognosis.

These findings are highly supported by current guidelines[49,82,83] and other authors[84-87] who do not recommend routine testing of asymptomatic patients, favoring instead, only selective use of imaging testing in high-risk groups of patients in a timeframe period of 3 to 6 months following PCI. These groups include patients with diabetes mellitus, decreased left ventricular ejection fraction, hazardous occupations, proximal left anterior descending artery disease, multivessel disease or multilesion PTCA and suboptimal PCI results. However, physicians do not appear to be adhering to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines for exercise testing regarding the routine use of post-PTCA functional testing and practice patterns vary widely among clinical centers, as shown by the ROSETTA registry that prospectively examined the use of functional testing strategy among 788 patients at 13 centers in 5 countries[88]. During the 6-month follow-up 49% of patients underwent functional testing, but among these only 39% had a clinical indication while the remaining patients had functional testing as a routine follow-up. None of the clinical characteristics identified by the ACC/AHA guidelines were associated with the routine use of post-PTCA functional testing, and the primary determinant of functional testing was the location of the center at which the patient had PTCA. It is important to note that more than two thirds of functional tests used involved the use of exercise treadmill testing alone in asymptomatic patients within 10 weeks of PTCA. The gross limits inherent to this approach are shown when considering that the positive predictive value of exercise testing in asymptomatic patients with single-vessel disease is as low as 18% and that restenosis may occur up to 6 months after PTCA (Fig. 3)[50].

Conclusions

Following PCI, functional stress imaging can be a valuable tool to assess patients who may benefit from further revascularization, and to document the short- and long-term results of such a therapy. As PCI is being used over and over in high-risk patients such as those with multivessel disease, occluded arteries, long lesions, vein graft, diabetes, acute coronary syndromes, restenosis rate is continuing to be a problem, despite the use of stents and more recently of drug-eluting stents. Also, partial revascularization is performed in some patients, especially in elderly and those with previous myocardial infarction, therefore leaving a potential source of ischemia irrespective of restenosis. In addition, patients may develop disease progression in vessels that were not significantly narrowed at the time of PTCA. The ability of functional imaging testing to diagnose restenosis accurately, and to differentiate it from other causes of myocardial ischemia (e.g. incomplete revascularization or progression of disease) whether symptomatic or not would undoubtedly assist in the management of patients after PCI. Furthermore, the clear superiority of stress imaging with regard to specificity and predictive value for post-revascularization events makes this functional approach of paramount importance in assessing prognosis of such patients. However, as predictive values of functional stress tests are highly dependent on the pre-test probability of disease, follow-up after PCI should always take into consideration the clinical characteristics of the patient (such as diabetes and age), the angiographic characteristics (severity of disease, myocardium at risk, left ventricular function), the procedural characteristics (length of the lesion, vessel size, number of stents implanted, etc.), symptoms and physical activity of the patient. All of these parameters together will assess the risk of the patient and will help to choose for the functional appropriate follow-up protocol.

References

1. Gruentzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979; 301: 61-8.
2. Serruys PW, Unger F, Sousa JE, et al, for the Arterial Revascularization Therapies Study Group. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001; 344: 1117-24.
3. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in patients with coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994; 331: 496-501.
4. Califf RM, Fortin DF, Frid DJ, et al. Restenosis after coronary angioplasty: an overview. J Am Coll Cardiol 1991; 17 (Suppl B): 2B-13B.
5. Mudra H, Di Mario C, de Jaegere P, et al, for the OPTICUS (Optimization With ICUS to Reduce Stent Restenosis) Study Investigators. Randomized comparison of coronary stent implantation under ultrasound or angiographic guidance to reduce stent restenosis (OPTICUS Study). Circulation 2001; 104: 1343-9.
6. O'Meara JJ, Dehmer GJ. Care of the patient and management of complications after percutaneous coronary artery interventions. Ann Intern Med 1997; 127: 458-71.
7. Mercado N, Boersma E, Wijns W, et al. Clinical and quantitative coronary angiographic predictors of coronary restenosis: a comparative analysis from the balloon-to-stent era. J Am Coll Cardiol 2001; 38: 645-52.
8. Moses JW, Leon MB, Popma JJ, et al, for the SIRIUS Investigators. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003; 349: 1315-23.
9. Lemos PA, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry. Circulation 2004; 109: 190-5.
10. 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.
11. Ruygrok PN, Webster MW, de Valk V, et al. Clinical and angiographic factors associated with asymptomatic restenosis after percutaneous coronary intervention. Circulation 2001; 104: 2289-94.
12. Nobuyoshi M, Kimura T, Nosaka H, et al. Restenosis after successful percutaneous coronary angioplasty: serial angiographic follow-up of 229 patients. J Am Coll Cardiol 1988; 12: 616-23.
13. Guiteras P, Tomas L, Varas C, et al. Five years of angiographic and clinical follow-up after successful percutaneous transluminal coronary angioplasty. Eur Heart J 1989; 10 (Suppl G): 42-8.
14. Holmes DR Jr, Vlietstra RE, Smith HC, et al. Restenosis after percutaneous transluminal coronary angioplasty (PTCA): a report from the PTCA Registry of the National Heart, Lung, and Blood Institute. Am J Cardiol 1984; 53: 77C-81C.
15. Hecht HS, Shaw RE, Chin HL, Ryan C, Stertzer SH, Myler RK. 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.
16. Hernandez RA, Macaya C, Iniguez A, et al. Midterm outcome of patients with asymptomatic restenosis after coronary balloon angioplasty. J Am Coll Cardiol 1992; 19: 1402-9.
17. Legrand V, Raskinet B, Laarman G, Danvhin N, Morel MA, Serruys PW. Diagnostic value of exercise electrocardiography and angina after coronary artery stenting. Benestent Study Group. Am Heart J 1997; 133: 240-8.
18. Giedd KN, Bergmann SR. Myocardial perfusion imaging following percutaneous coronary intervention: the importance of restenosis, disease progression, and directed reintervention. J Am Coll Cardiol 2004; 43: 328-36.
19. Popma JJ, van den Berg EK, Dehmer GJ. Long-term outcome of patients with asymptomatic restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1988; 62: 1298-9.
20. Pfisterer M, Rickenbacher P, Kiowski W, Muller-Brand J, Burkart F. Silent ischemia after percutaneous transluminal coronary angioplasty: incidence and prognostic significance. J Am Coll Cardiol 1993; 22: 1446-54.
21. Cottin Y, Rezaizadeh K, Touzery C, et al. Long-term prognostic value of 201Tl single-photon emission computed tomographic myocardial perfusion imaging after coronary stenting. Am Heart J 2001; 141: 999-1006.
22. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 1996; 335: 217-25.
23. Mock MB, Ringqvist I, Fisher LD, et al. Survival of medically treated patients in the Coronary Artery Surgery Study (CASS) registry. Circulation 1982; 66: 562-8.
24. Bourassa MG. Complete versus incomplete revascularization after percutaneous transluminal coronary angioplasty. In: Ellis SG, Holmes DR, eds. Strategic approaches in coronary intervention. Baltimore, FL: Williams and Wilkins, 1995: 440-4.
25. Vandormael MG, Chaitman BR, Ischinger T, et al. Immediate and short-term benefit of multilesion coronary angioplasty: influence of degree of revascularization. J Am Coll Cardiol 1985; 6: 983-91.
26. Wohlgelernter D, Cleman M, Highman HA, Zaret BL. Percutaneous transluminal coronary angioplasty of the "culprit lesion" for management of unstable angina pectoris in patients with multivessel coronary artery disease. Am J Cardiol 1986; 58: 460-4.
27. de Feyter PJ, Serruys PW, Arnold A, et al. Coronary angioplasty of the unstable angina related vessel in patients with multivessel disease. Eur Heart J 1986; 7: 460-7.
28. Kober G, Vallbracht C, Kadel C, Kaltenbach M. Results of repeat angiography up to eight years following percutaneous transluminal angioplasty. Eur Heart J 1989; 10 (Suppl G): 49-53.
29. Suresh CG, Grant SCD, Henderson RA, Bennett DH. Late symptom recurrence after successful coronary angioplasty: angiographic outcome. Int J Cardiol 1993; 42: 257-62.
30. 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.
31. Alderman EL, Kip KE, Whitlow PL, et al, for the Bypass Angioplasty Revascularization Investigation. Native coronary disease progression exceeds failed revascularization as cause of angina after five years in the Bypass Angioplasty Revascularization Investigation (BARI). J Am Coll Cardiol 2004; 44: 766-74.
32. Weintraub WS, Ghazzal ZM, Douglas JS Jr, et al. Long-term clinical follow-up in patients with angiographic

restudy after successful angioplasty. Circulation 1993; 87: 831-40.
33. Rupprecht HJ, Espinola-Klein C, Erbel R, et al. Impact of routine angiographic follow-up after angioplasty. Am Heart J 1998; 136 (Part 1): 613-9.
34. de Bono D. Complications of diagnostic cardiac catheterisation: results from 34 041 patients in the United Kingdom confidential enquiry into cardiac catheter complications. The Joint Audit Committee of the British Cardiac Society and Royal College of Physicians of London. Br Heart J 1993; 70: 297-300.
35. Devlin G, Lazzam L, Schwartz L. Mortality related to diagnostic cardiac catheterization. The importance of left main coronary disease and catheter induced trauma. Int J Card Imaging 1997; 13: 379-84.
36. Saito T, Date H, Taniguchi I, et al. Outcome of target sites escaping high-grade (> 70%) restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1999; 83: 857-61.
37. Gordon PC, Friedrich SP, Piana RN, et al. Is 40% to 70% diameter narrowing at the site of previous stenting or directional coronary atherectomy clinically significant? Am J Cardiol 1994; 74: 26-32.
38. Ferrari M, Schnell B, Werner GS, Figulla HR. Safety of deferring angioplasty in patients with normal coronary flow velocity reserve. J Am Coll Cardiol 1999; 33: 82-7.
39. Fischer JJ, Samady H, McPherson JA, et al. Comparison between visual assessment and quantitative angiography versus fractional flow reserve for native coronary narrowings of moderate severity. Am J Cardiol 2002; 90: 210-5.
40. Bech GJ, De Bruyne B, Pijls NH, et al. Fractional flow reserve to determine the appropriateness of angioplasty in moderate coronary stenosis: a randomized trial. Circulation 2001; 103: 2928-34.
41. Heller LI, Cates C, Popma J, et al. Intracoronary Doppler assessment of moderate coronary artery disease: comparison with 201Tl imaging and coronary angiography. FACTS Study Group. Circulation 1997; 96: 484-90.
42. Chamuleau SA, Tio RA, de Cock CC, et al. Prognostic value of coronary blood flow velocity and myocardial perfusion in intermediate coronary narrowings and multivessel disease. J Am Coll Cardiol 2002; 39: 852-8.
43. Flachskampf FA, Hoffmann R, vom Dahl J, Lethen H, Hanrath P. Functional assessment of PTCA results by stress echocardiography: when and how to test. Eur Heart J 1995; 16 (Suppl J): 31-4.
44. Kimura T, Yokoi H, Nakagawa Y, et al. Three-year follow-up after implantation of metallic coronary-artery stents. N Engl J Med 1996; 334: 561-6.
45. Asakura M, Ueda Y, Nanto S, et al. Remodeling of in-stent neointima, which became thinner and transparent over 3 years: serial angiographic and angioscopic follow-up. Circulation 1998; 97: 2003-6.
46. Schiele F. The "angioplastically correct" follow-up strategy after stent implantation. Heart 2001; 85: 363-4.
47. Violini R, Boschetti C, Fiorilli R. Dopo angioplastica: cadenza delle prove da sforzo e delle eventuali verifiche coronarografiche. In: Atti Conoscere e Curare il Cuore. Firenze: Essebiemme, 2004: 29-38.
48. Versaci F, Gaspardone A, Tomai F, et al. Chest pain after coronary artery stent implantation. Am J Cardiol 2002; 89: 500-4.
49. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to update the 1997 exercise testing guidelines). J Am Coll Cardiol 2002; 40: 1531-40.
50. Garzon P, Eisenberg MJ. Functional testing for the detection of restenosis after percutaneous transluminal coronary angioplasty: a meta-analysis. Can J Cardiol 2001; 17: 41-8.
51. Dori G, Denekamp Y, Fishman S, Bitterman H. Exercise stress testing, myocardial perfusion imaging and stress echocardiography for detecting restenosis after successful percutaneous transluminal coronary angioplasty: a review of performance. J Intern Med 2003; 253: 253-62.
52. Marie PY, Danchin N, Karcher G, et al. Usefulness of exercise SPECT-thallium to detect asymptomatic restenosis in patients who had angina before coronary angioplasty. Am Heart J 1993; 126 (Part 1): 571-7.
53. Milan E, Zoccarato O, Terzi A, et al. Technetium-99m-sestamibi SPECT to detect restenosis after successful percutaneous coronary angioplasty. J Nucl Med 1996; 37: 1300-5.
54. Kosa I, Blasini R, Schneider-Eicke J, et al. Myocardial perfusion scintigraphy to evaluate patients after coronary stent implantation. J Nucl Med 1998; 39: 1307-11.
55. Milavetz JJ, Miller TD, Hodge DO, Holmes DR, Gibbons RJ. Accuracy of single-photon emission computed tomography myocardial perfusion imaging in patients with stents in native coronary arteries. Am J Cardiol 1998; 82: 857-61.
56. Caner B, Oto A, Ovunc K, Kiratli P. Prediction of restenosis after successful percutaneous coronary angioplasty by dobutamine thallium-201 scintigraphy. Int J Cardiol 1998; 66: 175-81.
57. Beygui F, Le Feuvre C, Maunoury C, et al. Detection of coronary restenosis by exercise electrocardiography thallium-201 perfusion imaging and coronary angiography in asymptomatic patients after percutaneous transluminal coronary angioplasty. Am J Cardiol 2000; 86: 35-40.
58. Galassi AR, Foti R, Azzarelli S, et al. Usefulness of exercise tomographic myocardial perfusion imaging for detection of restenosis after coronary stent implantation. Am J Cardiol 2000; 85: 1362-4.
59. Manyari DE, Knudtson M, Kloiber R, Roth D. Sequential thallium-201 myocardial perfusion studies after successful percutaneous transluminal coronary artery angioplasty: delayed resolution of exercise-induced scintigraphic abnormalities. Circulation 1988; 77: 86-95.
60. Jain A, Mahmarian JJ, Borges-Neto S, et al. Clinical significance of perfusion defects by thallium-201 single photon emission tomography following oral dipyridamole early after coronary angioplasty. J Am Coll Cardiol 1988; 11: 970-6.
61. Hardoff R, Shefer A, Gips S, et al. Predicting late restenosis after coronary angioplasty by very early (12 to 24 h) thallium-201 scintigraphy: implications with regard to mechanisms of late coronary restenosis. J Am Coll Cardiol 1990; 15: 1486-92.
62. Rodes-Cabau J, Candell-Riera J, Domingo E, et al. Frequency and clinical significance of myocardial ischemia detected early after coronary stent implantation. J Nucl Med 2001; 42: 1768-72.
63. Versaci F, Tomai F, Nudi F, et al. Differences of regional coronary flow reserve assessed by adenosine thallium-201 scintigraphy early and six months after successful percutaneous transluminal coronary angioplasty or stent implantation. Am J Cardiol 1996; 78: 1097-102.
64. Wilson RF, Johnson MR, Marcus ML, et al. The effect of coronary angioplasty on coronary flow reserve. Circulation 1988; 77: 873-85.
65. Uren NG, Crake T, Lefroy DC, de Silva R, Davies GJ, Maseri A. Delayed recovery of coronary resistive vessel function after coronary angioplasty. J Am Coll Cardiol 1993; 21: 612-21.
66. Fioretti PM, Pozzoli MM, Ilmer B, et al. Exercise echocardiography versus thallium-201 SPECT for assessing pa-

tients before and after PTCA. Eur Heart J 1992; 13: 213-9.
67. Mertes H, Erbel R, Nixdorff U, Mohr-Kahaly S, Kruger S, Meyer J. Exercise echocardiography for the evaluation of patients after nonsurgical coronary artery revascularization. J Am Coll Cardiol 1993; 21: 1087-93.
68. Davila-Roman VG, Wong AK, Li D, et al. Usefulness of dobutamine stress echocardiography for the prospective identification of the physiologic significance of coronary narrowings of moderate severity in patients undergoing evaluation for percutaneous transluminal coronary angioplasty. Am J Cardiol 1995; 76: 245-9.
69. Hecht HS, DeBord L, Shaw R, et al. Usefulness of supine bicycle stress echocardiography for detection of restenosis after percutaneous transluminal coronary angioplasty. Am J Cardiol 1993; 71: 293-6.
70. Pirelli S, Danzi GB, Massa D, et al. Exercise thallium scintigraphy versus high-dose dipyridamole echocardiography testing for detection of asymptomatic restenosis in patients with positive exercise tests after coronary angioplasty. Am J Cardiol 1993; 71: 1052-6.
71. Bolognese L, Antoniucci D, Rovai D, et al. Myocardial contrast echocardiography versus dobutamine echocardiography for predicting functional recovery after acute myocardial infarction treated with primary coronary angioplasty. J Am Coll Cardiol 1996; 28: 1677-83.
72. Miller DD, Liu P, Strauss HW, Block PC, Okada RD, Boucher CA. Prognostic value of computer-quantitated exercise thallium imaging early after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1987; 10: 275-83.
73. Stuckey TD, Burwell LR, Nygaard TW, Gibson RS, Watson DD, Beller GA. Quantitative exercise thallium-201 scintigraphy for predicting angina recurrence after percutaneous transluminal coronary angioplasty. Am J Cardiol 1989; 63: 517-21.
74. Meluzin J, Cerny J, Frelich M, et al. Prognostic value of the amount of dysfunctional but viable myocardium in revascularized patients with coronary artery disease and left ventricular dysfunction. J Am Coll Cardiol 1998; 32: 912-20.
75. Afridi I, Grayburn PA, Panza JA, Oh JK, Zoghbi WA, Marwick TH. Myocardial viability during dobutamine echocardiography predicts survival in patients with coronary artery disease and severe left ventricular systolic dysfunction. J Am Coll Cardiol 1998; 32: 921-6.
76. Alazraki NP, Krawczynska EG, Kosinski AS, et al. Prognostic value of thallium-201 single-photon emission computed tomography for patients with multivessel coronary artery disease after revascularization (the Emory Angioplasty versus Surgery Trial - EAST). Am J Cardiol 1999; 84: 1369-74.
77. Parisi A, Hartigan PM, Folland ED. Evaluation of exercise thallium scintigraphy versus exercise electrocardiography in predicting survival outcomes and morbid cardiac events in patients with single- and double-vessel disease. Findings from the Angioplasty Compared to Medicine (ACME) Study. J Am Coll Cardiol 1997; 30: 1256-63.
78. Galassi AR, Azzarelli S, Tomaselli A, et al. Incremental prognostic value of technetium-99m-tetrofosmin exercise myocardial perfusion imaging for predicting outcomes in patients with suspected or known coronary artery disease. Am J Cardiol 2001; 88: 101-6.
79. Galassi AR, Grasso C, Azzarelli S, et al. Usefulness of exercise myocardial scintigraphy in multivessel coronary disease after incomplete revascularization with coronary stenting. Am J Cardiol, in press.
80. Galassi AR, Grasso C, Leotta E, et al. Usefulness of routine exercise SPECT myocardial scintigraphy after revascularization with coronary stenting in high risk-patients. (abstr) Eur Heart J 2004; 25 (Suppl): 1564.
81. Ho KT, Miller TD, Holmes DR, Hodge DO, Gibbons RJ. Long-term prognostic value of Duke treadmill score and exercise thallium-201 imaging performed one to three years after percutaneous transluminal coronary angioplasty. Am J Cardiol 1999; 84: 1323-7.
82. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to revise the 1995 guidelines for the clinical use of cardiac radionuclide imaging). J Am Coll Cardiol 2003; 42: 1318-33.
83. Smith SC, Dove JT, Jacobs AK, et al. ACC/AHA guidelines for percutaneous coronary intervention (revision of the 1993 PTCA guidelines): executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1993 guidelines for percutaneous transluminal coronary angioplasty). J Am Coll Cardiol 2001; 37: 2215-39.
84. Manyari DE, Dzavik V. Stress testing after percutaneous coronary interventions. Can J Cardiol 2000; 16: 734-8.
85. Miller DD, Verani MS. Current status of myocardial perfusion imaging after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1994; 24: 260-6.
86. Krone RJ, Hardison RM, Chaitman BR, et al. Risk stratification after successful coronary revascularization: the lack of a role for routine exercise testing. J Am Coll Cardiol 2001; 38: 136-42.
87. Eisenberg MJ, Blankenship JC, Huynh T, et al, for the ADORE Investigators. Evaluation of routine functional testing after percutaneous coronary intervention. Am J Cardiol 2004; 93: 744-7.
88. Eisenberg MJ, Schechter D, Lefkovits J, et al, for the ROSETTA Investigators. Use of routine functional testing after percutaneous transluminal coronary angioplasty: results from the ROSETTA Registry. Am Heart J 2001; 141: 837-46.

CEPI - AIM Group

Centro Editoriale Pubblicitario Italiano
via A. Ristori, 38 - 00197 Rome, Italy
tel. +39-06.80968324-80968322, fax +39-06.8072458
e-mail: info.cepi@aimgroup.it, internet: www.aimgroup.it

Chief Executive Officer
Gianluca Buongiorno

Product Manager
Marinella Buongiorno

Head, Editorial Office
Paola Luciolli

Editorial Office
Roberta Canali
Letizia Capitanini

Business Office
Mirella Federici

Subscription Department
Angela Perazzini

Accounts Department
Angela Perazzini