

# Prognostic Value of “Routine” Cardiac Stress Imaging 5 Years After Percutaneous Coronary Intervention

## The Prospective Long-Term Observational BASKET (Basel Stent Kosteneffektivitäts Trial) LATE IMAGING Study

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**Objective** This study sought to evaluate the prognostic value of routine stress myocardial perfusion scintigraphy (MPS) 5 years after percutaneous coronary intervention (PCI).

**Background** Current appropriate use criteria define routine cardiac stress imaging <2 years after PCI as inappropriate and >2 years as uncertain in asymptomatic patients.

**Methods** All 339 of 683 BASKET (Basel Stent Kosteneffektivitäts Trial) 5-year survivors (55%) consenting to undergo protocol-mandated MPS and subsequent evaluation irrespective of symptoms were followed for major adverse cardiac events (MACE) (cardiac death, myocardial infarction [MI], or revascularization). For MPS, summed perfusion scores were calculated and perfusion defects were related to treated-vessel or remote myocardial areas.

**Results** Patients were  $72 \pm 10$  years of age, 18% were female, and 90% were free of angina. MPS findings were abnormal in 205 of 339 patients (60%) with complete follow-up. During  $3.7 \pm 0.3$  years, there were 7 cardiac deaths, 18 MIs, and 47 revascularizations, resulting in a MACE rate of 4.4% and a cardiac mortality rate of 0.6% per year. Patients with abnormal MPS findings had higher hazard ratios (HR) for MACE (HR: 1.95; 95% confidence interval [CI]: 1.06 to 3.59;  $p = 0.032$ ), and cardiac death/MI (HR: 2.50; 95% CI: 0.93 to 6.69;  $p = 0.066$ ) than patients with normal MPS finding. MACE rates were similar in patients with symptomatic and silent ischemia ( $p = 0.61$ ) but higher than in patients with normal MPS findings ( $p < 0.05$  for both comparisons). MACE rates were independently predicted by remote ischemia but not by treated-vessel ischemia or scar.

**Conclusions** Abnormal MPS findings 5 years after PCI are frequent irrespective of symptoms. The predictive power of abnormal MPS lies more in the detection of persistent or progressing coronary artery disease in remote vessel areas than in the diagnosis of late intervention-related problems in treated vessels. (J Am Coll Cardiol Intv 2014;7:615–21) © 2014 by the American College of Cardiology Foundation

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Coronary artery disease (CAD) remains a progressive disease after successful percutaneous coronary intervention (PCI) and stent implantation, as recently demonstrated 3 to 5 years after the PCI (1,2). If progression or problems related to the previous PCIs lead to recurrent symptoms, then stress imaging is recommended according to European and U.S. guidelines (3,4). Relevant ischemia should then trigger the performance of coronary angiography and, if possible and feasible, repeat revascularization. Early after the intervention (i.e., up to 6 months), positive findings on single-photon emission computed tomography myocardial perfusion scintigraphy (MPS) have been shown to predict future events (5,6). However, routine stress testing (i.e., testing also in patients without recurrent symptoms) is not advised (7,8), except for special high-risk patient groups (9). Therefore, in currently valid guidelines for appropriate use of stress imaging after PCI, routine stress imaging >2 years after the intervention has been termed uncertain in asymptomatic

patients on the basis of a lack of corresponding data (10,11). On the other hand, a U.S. Food and Drug Administration expert panel recommended 5-year outcome studies for drug-eluting stent safety (12), but up to that point in time, progression or new development of CAD may become as relevant as very late stent-related problems, as recently shown (1,2). Still, the prognostic relevance of such a very late assessment is unknown.

It was, therefore, the aim of the present prospective BASKET (Basel Stent Kosteneffektivitäts Trial) LATE IMAGING study

to define the prognostic value of stress MPS 5 years after successful PCI in a large, well-characterized all-comer PCI population, irrespective of symptoms, to predict future cardiac events.

## Methods

**Patients.** All 683 consecutive patients surviving to 5 years after successful stent implantation of the original BASKET population were invited to undergo a stress MPS study. Initially, the BASKET included 826 consecutive patients in need of PCI and stenting between May 5, 2003 and May 31, 2004, at the University Hospital of Basel, Switzerland, and randomized them in a 2:1 fashion to drug-eluting versus bare-metal stents (13). Figure 1 shows that the present study population consisted of 372 patients (55% of all 683 possibly available patients or 45% of the entire initial BASKET population). Of these, 5 patients withdrew consent and 28 were lost during the  $3.7 \pm 1.3$ -year follow-up, leaving

339 patients (91% of the study population) with complete outcome data, forming the present prognostic study patient population.

**Stress myocardial perfusion imaging.** Stress MPS studies were performed following a standard protocol and read by specialists in nuclear cardiology independent of this study as previously described (1,6). In short, a rest-stress dual-isotope (thallium-201/technetium-99m sestamibi) protocol with exercise or pharmacological (adenosine) stress and electrocardiographic monitoring was used after withdrawal of antianginal drugs if possible. Images were scored using a 17-segment model with a 5-point scale of 0 (normal) to 4 (no uptake). Summed stress, rest, and difference scores were calculated. At the time of this MPS study, all patients underwent a clinical visit as the baseline for the present prospective study.

**Follow-up.** At 3 to 4 years after the 5-year MPS study, all patients were contacted to answer a dedicated questionnaire asking about cardiac events, specifically cardiac death, myocardial infarction (MI), and repeat revascularization as well as current symptoms and medications between the 5-year MPS study and the final follow-up. If patients could not be reached or specific data were missing, relatives and/or private physicians were contacted to verify survival status and, if applicable, to assess the cause of death. In addition, hospital charts were collected for patients hospitalized during follow-up and private physicians' charts were consulted to verify endpoints.

All patients were asked to provide (new) written informed consent for the present study and for the use of their data. The study protocol for this study was approved by the Ethical Committee of the 2 states of Basel.

**Definitions.** The primary endpoint of this prospective BASKET LATE IMAGING study was major adverse cardiac events (MACE) (i.e., cardiac death, nonfatal MI, and repeat revascularization) during follow-up in relation to MPS findings (normal or abnormal MPS findings in the 5-year MPS study). Cardiac deaths, documented MIs according to standard definitions used in BASKET (13), and all repeat revascularization procedures (PCI and coronary artery bypass graft surgery) during follow-up were considered. All revascularizations were counted as endpoints because revascularization beyond 60 days after testing generally is considered to be a new event not triggered by test results and because 7 of 8 early revascularizations (<60 days) in the current study were performed for an acute coronary syndrome ( $n = 1$ ) or extensive ischemia (mean summed difference score [SDS] was 7.6) with prognostic relevance (14–16). Secondary endpoints were individual components of the primary endpoint each separately and the combined endpoint of cardiac death/MI. Angina pectoris was deemed present if reported as typical chest pain or, in patients with uncertain pain, if typical angina occurred during the stress test. For MPS studies, a defect score

### Abbreviations and Acronyms

**CAD** = coronary artery disease

**CI** = confidence interval

**HR** = hazard ratio

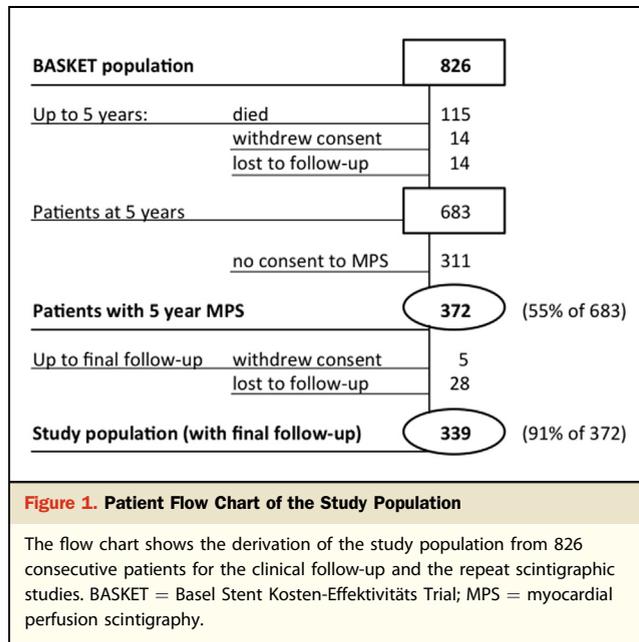
**MACE** = major adverse cardiac event(s)

**MI** = myocardial infarction

**MPS** = myocardial perfusion scintigraphy

**PCI** = percutaneous coronary intervention

**SDS** = summed difference score



that affected  $\geq 5\%$  myocardium was considered significant (1). Overall abnormality (i.e., reversible defects indicating ischemia and fixed defects indicating scar) was evaluated. Defects in the myocardial area of the initially treated vessel(s) were labeled treated-vessel defects and those in other myocardial regions remote defects.

**Analyses.** In a first step, baseline characteristics of the present study population were compared with the original BASKET population; the 33 patients without final follow-up information were evaluated separately. Then the 5-year baseline characteristics of the prognostic cohort were compared between those with versus without a positive MPS result. For outcome analyses, the primary and secondary endpoints were determined with regard to the MPS result. Then, MACE rates of subgroups of patients with versus without angina pectoris, those of patients with symptomatic versus silent ischemia as well as for patients with treated-vessel versus remote ischemia, respectively, were analyzed.

**Statistics.** Data are presented as mean  $\pm$  SD or percentages as appropriate. The groups were compared with the Fisher exact test for categorical variables and the unpaired Student *t* test for numeric variables. Cumulative hazard curves were used to compare outcomes between patient groups using the log-rank test. Hazard ratios (HRs)  $\pm$  95% confidence intervals (CIs) were calculated using a Cox regression model. Cox regression models were also used to identify significant univariate and multivariate predictors of endpoints. All significantly different parameters in baseline variables (Table 1: age, sex, ST-segment elevation MI at baseline, multivessel disease at baseline, left ventricular ejection fraction [at 5-year MPS], treated-vessel ischemia, and remote ischemia) were used for the primary endpoint MACE, and age, LVEF and the extent of ischemia by MPS (SDS) (all at the 5-year baseline)

**Table 1. Five-Year Baseline Characteristics of the Prognostic Study Patient Population With Normal as Compared With Abnormal Scintigraphic Findings**

Baseline	Normal MPS (n = 134)	Abnormal MPS (n = 205)	p Value
Age, yrs	71 $\pm$ 9	73 $\pm$ 10	0.042
Male	73	88	0.001
Previous MI	10	36	<0.001
Diabetes	16	13	0.53
Hyperlipidemia	81	82	1.00
Hypertension	66	61	0.42
Smoking	22	21	1.00
STEMI*	11	22	0.008
ACS*	32	40	0.11
Chronic CAD*	57	37	0.003
Multivessel disease	52	73	<0.001
BMS use	31	31	1.00
Angina at 5-yr MPS	10	11	0.719
LVEF at 5-yr MPS	63 $\pm$ 7	51 $\pm$ 11	<0.001

Values are mean  $\pm$  SD or %. \*The initial BASKET intervention.

ACS = acute coronary syndromes; BMS = bare metal stent; CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MPS = myocardial perfusion scintigraphy; STEMI = ST-segment elevation myocardial infarction.

for the secondary endpoint of cardiac death/MI. A value of  $p < 0.05$  was considered statistically significant. SPSS software version 21 (IBM Inc., Armonk, New York) was used. **Role of the funding source.** The Swiss Heart Foundation had no role whatsoever in the design, conduct, or interpretation of this study.

## Results

**Patients and baseline characteristics.** The main characteristics of the present study population with outcome information (n = 339) at BASKET baseline (i.e., 5 years before the start of the present study), are compared with BASKET patients not participating in the present study in Table 2. Because the latter contained all 115 patients who died during these 5 years, the present study population was somewhat younger and more often male and had less often ST-segment elevation MI and multivessel disease as presenting problems, with some additional differences in coronary risk factors. Study patients were 72  $\pm$  10 years of age, 18% were female, and 90% were free of angina at the time of the 5-year follow-up MPS. **MPS findings.** Stress was performed by bicycle ergometry alone in 69% of patients and by pharmacological stress with adenosine infusion in 31%. A significant perfusion defect (scar or ischemia) was noted in 205 of 339 patients (60%), defects being fixed (scar) only in 139 patients, reversible only (ischemia) in 58 patients, and combined fixed and reversible (scar and ischemia) in 8 patients. Of the reversible perfusion defects (ischemia), 55% were attributed to the initially treated vessels, 33% to remote regions, and 12% to both.

**Table 2. Baseline Characteristics (at BASKET Baseline) of the Prognostic Study Population in Relation to the Total BASKET Population and BASKET Patients Without 5-Year Follow-up**

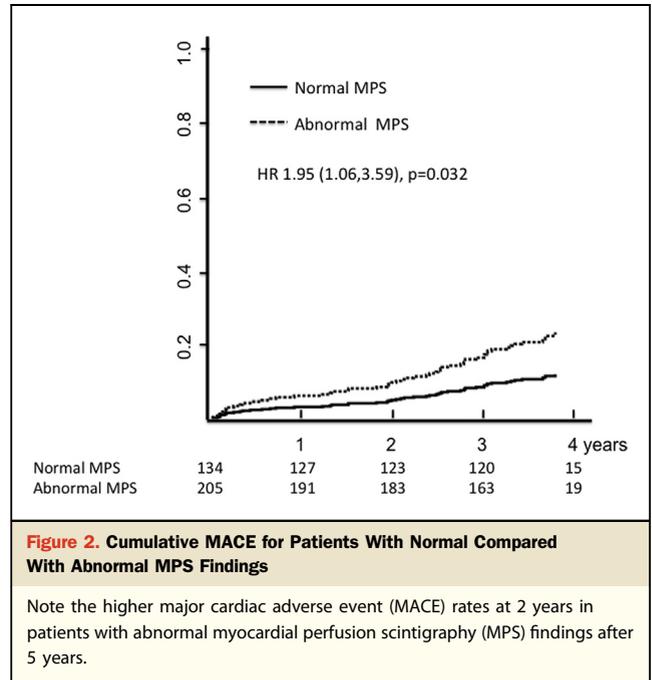
Baseline	All BASKET (n = 826)	No 5-Yr Follow-up (n = 487)	5-Yr Follow-up (n = 339)	p Value
Age, yrs	64 ± 11	65 ± 12	63 ± 10	0.01
Male	79	76	82	0.05
Previous MI	27	29	26	0.383
Diabetes	19	22	14	0.005
Hyperlipidemia	75	70	82	<0.001
Hypertension	67	68	63	0.155
Smoking	28	33	22	<0.001
STEMI*	21	24	18	0.05
ACS*	36	36	37	0.72
Chronic CAD*	42	40	45	0.21
Multivessel disease	70	71	65	0.051
BMS use	34	36	31	0.136

Values are mean ± SD or %. \*The initial BASKET intervention.  
ACS = acute coronary syndromes; BMS = bare metal stent; CAD = coronary artery disease; STEMI = ST-segment elevation myocardial infarction.

Baseline characteristics of the prognostic patient population (n = 339) at the time of the MPS study are compared in Table 1 in relation to MPS study results. Patients with an abnormal MPS result were older and more often male and more often had a previous MI, also ST-segment elevation MI as a presenting problem 5 years earlier together with a higher rate of multivessel coronary disease at that point in time. Thus, scintigraphically determined left ventricular ejection fraction at the time of the 5-year MPS study was lower in patients with an abnormal MPS result. However, the rates of angina at 5 years and at final follow-up were not different (Table 1, Online Table 1). The same held true for the medications at final follow-up (Online Table 1).

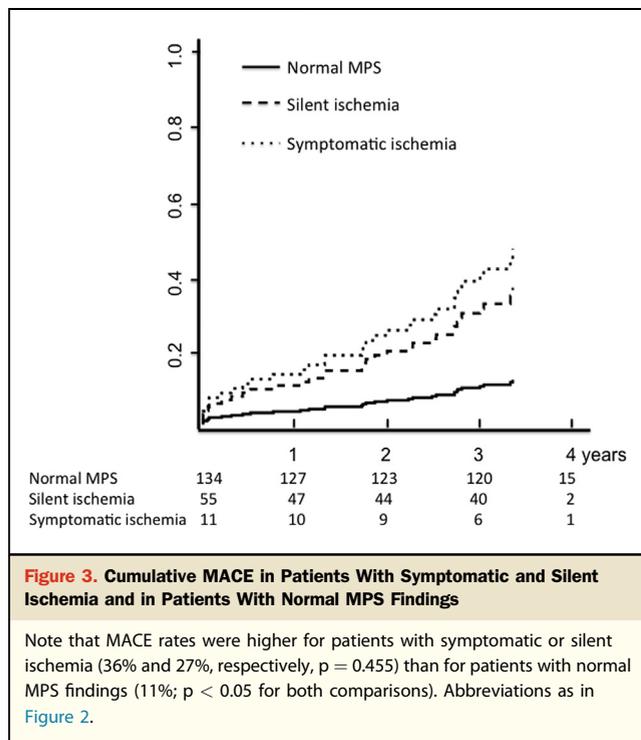
Corresponding data for the 33 patients withdrawing consent or lost to long-term follow-up did not differ from the total prognostic population except for rates of diabetes and smoking, and their MPS findings were not different from those of patients in the prognostic cohort (Online Table 2).

**Follow-up events in relation to MPS findings.** During a mean follow-up of  $3.7 \pm 1.3$  years (range, 3.1 to 4.8 years) in the 339 patients with complete follow-up information, 7 cardiac deaths, 7 noncardiac deaths, 18 documented MIs, and 47 repeat revascularization procedures (38 PCIs, 9 surgeries) were reported. Overall, 55 patients had at least 1 MACE, for a cardiac event rate of 4.4% per year of follow-up or a cardiac mortality rate of 0.6% per year. Patients with abnormal MPS findings had a higher cumulative MACE rate (HR: 1.95; 95% CI: 1.06 to 3.59;  $p = 0.032$ ), as shown in Figure 2, as well as a trend to a higher cardiac death/MI rate (HR: 2.50; 95% CI: 0.93 to 6.69;  $p = 0.066$ ) than



patients with normal findings. The annual cardiac death rate was not statistically different in patients with versus without normal MPS findings (0.2% and 0.8%, respectively,  $p = 0.252$ ). Note that normal findings on MPS predicted an excellent outcome with a yearly MACE rate of only 3% and a cardiac mortality rate of 0.2% per year of follow-up. The only independent predictor of cardiac death/MI was the extent of ischemia (SDS per point) (HR: 1.16; 95% CI: 1.07 to 1.26;  $p < 0.001$ ).

**Findings in relation to symptomatic or silent ischemia and localization of ischemia.** Any scintigraphic ischemia as defined for this study was detected in 66 patients (19.5%). The MACE rate in patients with ischemia was higher than in those without ischemia (HR: 2.65; 95% CI: 1.51 to 4.65;  $p = 0.001$ ). In these 66 patients, ischemia was symptomatic in 17% and silent in 83% (16% of the total prognostic patient population). Figure 3 shows that cumulative rates of MACE were similar in patients with symptomatic (36%) and silent (27%) ischemia ( $p = 0.610$ ) but higher than in patients with normal findings on MPS (11%) ( $p < 0.05$  for both). However, the outcome was not influenced by presence of scintigraphic scar (16% MACE rate, both in patients with and without scar). The MACE rate in patients with treated-vessel ischemia was 19%, not significantly different from that of patients without this finding (16%;  $p = 0.629$ ), whereas the MACE rate of patients with remote ischemia was higher than that of patients without remote ischemia (41% vs. 14%,  $p = 0.003$ ). In the Cox regression analysis, remote ischemia was the only independent predictor of MACE (HR: 4.1; 95% CI: 1.97 to 8.37;  $p < 0.001$ ).



## Discussion

These findings of the BASKET LATE IMAGING study document a strong prognostic value of routine stress imaging 5 years after successful PCI and stent implantation, irrespective of recurrent symptoms. It is the first reasonably sized prospective study evaluating the prognostic value of routine stress MPS 5 years after PCI in patients selected neither for symptoms nor for particularly high risk. Importantly, the outcome of patients with normal MPS findings was excellent, but the prevalence of silent ischemia was high and its predictive power for future events similar to that of symptomatic ischemia. The observation that there was an independently predictive value of remote compared with treated-vessel ischemia 5 years after the intervention indicates that, at this point in time, progression of CAD in remote vessel areas seems to be more relevant than late intervention-related treated-vessel problems.

Previous studies on stress imaging after PCI focused on the early period within the first year after the intervention only or primarily on symptomatic patients (5,17–22). The results of these studies were controversial, leading to the recommendation that routine stress testing of asymptomatic patients <2 years after the intervention should not be performed without specific indications (23,24). In predicting future events very late after PCI, one has to consider that at this point in time, patients are elderly (>70 years of age), such that mortality was as high for extracardiac as for cardiac causes in the present study; that patients presented in

a stable condition, indicating that overall yearly event rates are low (4.4% for MACE and 2% for cardiac death/MI in the present study); and that >90% of patients were asymptomatic, such that for them, symptoms leading to the need for (repeat) revascularization was a major event. Note that new relevant symptoms often reflect CAD progression, which may manifest as new or increasing vessel obstructions rather than abrupt vessel closures. Only the extent of ischemia (SDS) predicted the secondary endpoint of cardiac death/MI, whereas only remote ischemia independently predicted follow-up MACE. This suggests that very late after PCI, progression of CAD becomes prognostically more important than stent-related problems, a finding that is equally important for stent safety assessments as for patients: it implies the need for continued intense secondary prevention of CAD.

Although the aim of the original BASKET was to achieve full revascularization in all patients (13), which was documented after 6 months in 93% of available patients for follow-up MPS (6), it cannot be verified that ischemia after 5 years was due to not fully revascularized CAD at BASKET baseline or whether it all was due to progression of minimal disease or new development of significant lesions. A recent specific analysis showed that in fact progression or new development of CAD is relevant late (5 years) after revascularization (1). However, this differentiation seems of limited relevance in view of the prognostic importance of such a test if performed in unselected post-stenting patients.

The question remains unanswered whether patients with silent ischemia, as detected at a high rate in the present study, should be managed by repeat intervention or optimized medical therapy to improve outcomes similar to patients with symptomatic ischemia. Two small randomized trials, the ACIP (Asymptomatic Coronary Ischemia Pilot) study (25) and the SWISSI (Swiss Interventional Study on Silent Ischemia) II (26) suggested that repeat revascularization improves prognosis in patients with silent ischemia. A recent nonrandomized study in 769 asymptomatic patients with previous revascularization and inducible ischemia detected by myocardial perfusion imaging questioned this notion because 15% of patients selected for repeat revascularization had no survival benefit compared with 85% of patients selected for medical therapy (23). However, this study was subject to a major selection bias: in patients with a coronary anatomy already known from an average of 2 previous revascularizations, the clinical decision to perform another revascularization will rarely depend only on the presence or absence of myocardial ischemia at follow-up. Remaining options for revascularization, willingness of patients to undergo a further intervention despite the absence of symptoms, comorbidities, and whether these patients were fully revascularized initially or tested before entering a rehabilitation program or before noncardiac surgery are just

some of the factors that were missed, even with multiple statistical adjustments to account for treatment group differences.

Another recent observational study in which only 34% of 262 patients with exercise ischemia after revascularization were selected for repeat revascularization were subject to similar limitations (23). Both studies and an invited comment on the basis of 2 older studies (27) concluded that patients at increased risk may be detected, but that they do not seem to benefit from repeat revascularization such that routine testing in asymptomatic patients may not be justified (24,28). However, only large randomized, controlled trials will be able to answer the question of how the outcomes of patients with silent ischemia can be improved, an outcome that was similar to that of symptomatic ischemia in the present study years after PCI (22). Perhaps the ongoing ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) or the TIME-DM (Trial of Invasive versus Medical therapy of Early coronary artery disease in Diabetes Mellitus) will be able to answer part of this question. A general recommendation to perform a routine ischemia test late after PCI and stenting would, therefore, only be justified if a dedicated treatment trial would show a benefit of treating such patients with mainly silent ischemia, taking into account a cost-benefit evaluation. Thus, present findings do not call for routine testing in all such patients but highlight the importance of CAD progression 5 years after PCI, often occurring silently, and its impact on long-term outcome.

**Study limitations.** Limitations of this noninvasive follow-up study relate to the fact that coronary angiographic data were not available in any of these patients at the time of the 5-year MPS study. Thus, anatomic mechanisms underlying observed perfusion defects remain undefined. This would be particularly interesting in the treated-vessel area to differentiate a restenotic process from CAD progression in the same vessel distant to the treated segment. However, some patients were not available for the 5-year MPS study, and some could not be located for the final follow-up, almost 9 years after the BASKET intervention. Still, the rate of patients available for these investigations was remarkably high (91%) and only possible in a stationary population as typical for our region. In addition, the comparison of baseline data documented that the present study population was fairly representative of what could be expected 5 years after an intervention. Note, however, that secondary prevention was not optimal, although the rate of antiplatelet, statin, and beta-blocker drugs was high (>70% to 90%) for mostly asymptomatic patients in an observational long-term trial. Finally, we cannot extrapolate from these results whether similar findings could have been found 2, 3, or 4 years after PCI already or whether findings would have been similar in 1-vessel PCI patients. The observation that 5 years after the intervention the prognostic value of treated-vessel ischemia was lower than that

of remote ischemia indicates that the reason for late cardiac stress imaging may be the detection of persistent or progressive CAD rather than very late intervention-related problems.

## Conclusions

BASKET LATE IMAGING documents the prognostic value of routine cardiac stress imaging 5 years after successful PCI and stent implantation irrespective of recurrent symptoms. Its predictive power lies more in the detection of persistent or progressive CAD in remote-vessel areas than in the diagnosis of very late intervention-related problems in the treated vessels. Findings emphasize the importance of long-term secondary prevention of CAD and call for a randomized, controlled trial to define the optimal management of patients with ischemia very late after revascularization, irrespective of symptoms, and its cost-benefit implications.

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- Key Words:** CAD progression ■ cardiac imaging ■ coronary artery disease ■ long-term outcome ■ myocardial perfusion scintigraphy ■ percutaneous coronary intervention ■ risk stratification ■ silent ischemia.
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- APPENDIX**
- For supplemental tables, please see the online version of this article.