

CLINICAL RESEARCH

Coronary Artery Disease

## Coronary Artery Disease Progression Late After Successful Stent Implantation

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- Objectives** This study sought to define the importance of 5-year coronary artery disease (CAD) progression after successful stenting.
- Background** Safety concerns regarding first-generation drug-eluting stents mandate 5-year follow-up studies. However, only limited data exist on the long-term importance of CAD progression relative to late stent-related problems.
- Methods** This study followed for 5 years, 428 consecutive patients randomized to drug-eluting versus bare-metal stents with successful stenting documented by freedom from symptoms/events and no ischemic perfusion defects (PDs) after 6 months. Rest/stress scintigraphic scans were repeated after 60 months. Late events and new PDs in areas remote from stented vessels indicated CAD progression.
- Results** During follow-up, 110 of 428 (25.7%) patients had 150 clinical events: 43 patients (10%) died, 36 (8.4%) suffered a myocardial infarction, and 71 (16.6%) needed repeat revascularization. Event rates were lower in remote versus target-vessel areas (9.8% vs. 14.3%,  $p = 0.019$ ). Remote myocardial infarction and repeat revascularization accounted for 46 of 124 (37.1%) nonfatal events and were similar for both stent types. Five-year scintigraphic studies in patients without follow-up events showed 23.3% new PDs, 71% of which were asymptomatic. Remote defects accounted for 37.5% PDs and were similar for both stent types.
- Conclusions** Even 5 years after stenting, target-vessel events and/or new PDs remained more frequent than CAD progression assessed by remote events and/or new PDs. Still, remote events accounted for almost 40% of all events with a similar rate of additional new PDs, often silent, and independent of stent type. This documents the importance of CAD progression and stresses the need to differentiate remote from target-vessel events/PDs in long-term stent safety studies. (Basel Stent Kosten-Effektivitäts Trial [BASKET]; ISRCTN75663024) (J Am Coll Cardiol 2012;59:793-9) © 2012 by the American College of Cardiology Foundation

Safety concerns regarding late cardiac death or nonfatal myocardial infarction (MI) related to late stent thrombosis mandate prolonged follow-up after implantation of first-generation drug-eluting stents (DES) (1). Late stent thromboses occurring after 6 to 12 months after the intervention, first observed in individual patients (2), were found to occur more often after DES than after bare-metal stent (BMS) use in the “all-comer” angioplasty population of the BASKET

(Basel Stent Kosten-Effektivitäts Trial) (3). The rate was low and did not affect overall mortality. This was confirmed in several studies and registries (4,5) with rates of definite stent thrombosis according to the Academic Research Consortium’s definitions (6) after DES implantation of approximately 0.6% per year, steadily increasing up to 4

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years of follow-up (7). Still, 5-year follow-up reports of the pivotal DES trials (8,9) confirmed the benefits of first-generation DES, compared with BMS, in reducing target-vessel (TV) revascularization without increasing overall death or MI rates.

In view of the progressive nature of coronary artery disease (CAD), it could be expected that during prolonged follow-up investigations after stenting, cardiac events would occur irrespective of this procedure in vessels or locations

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**Abbreviations and Acronyms**

- BMS** = bare-metal stent(s)
- CAD** = coronary artery disease
- DES** = drug-eluting stent(s)
- MI** = myocardial infarction
- PDs** = perfusion defects
- SPECT** = single-photon emission computed tomography
- TV** = target vessel

not touched by the intervention. In a low-risk clinical trial population treated with BMS, hazard rates for late non-TV events were about 3 times higher than for TV events (10). In long-term follow-up investigations of pooled early DES trials (11,12), events attributed to non-TVs were estimated at 26% during years 2 to 5 after the intervention, with similar rates in DES- and BMS-treated patients. However, these findings were based on observations of

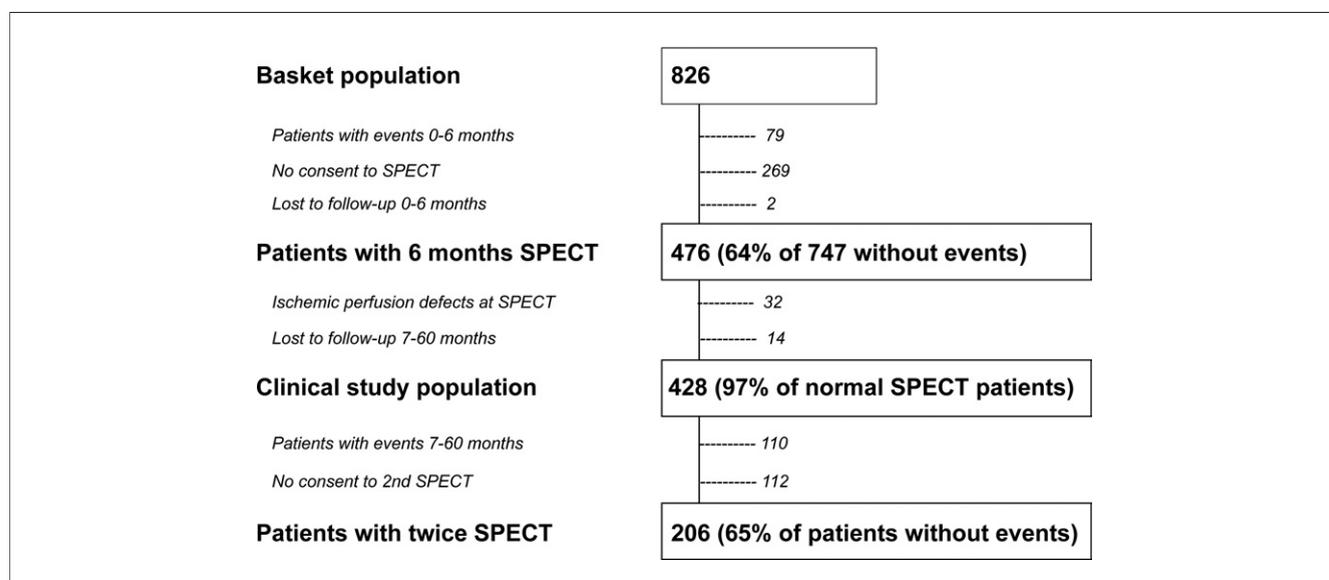
low-risk patients and influenced by protocol-driven repeat coronary angiographies and limited follow-up rates. Importantly, in a broader population of patients including those with multivessel disease, the importance of CAD progression can only be assessed if the initial revascularization is shown to be successful and complete. In addition, disease progression may not only manifest as death, remote MI, and angina-driven non-TV revascularization, but also as symptomatic or silent new perfusion defects (PDs).

Thus, the aim of the present prospective investigation was to define the importance of CAD progression over a 5-year period after successful complete revascularization by angioplasty and stenting in a comprehensive manner capturing clinically symptomatic and silent disease and comparing it between patients randomized to DES versus BMS. We hypothesized that during late follow-up, clinical CAD progression could become as relevant as symptomatic late stent problems occurring irrespective of stent type implanted.

**Methods**

**Patients and study design.** BASKET included 826 consecutive patients treated with angioplasty and stenting between May 2003 and May 2004 at the University Hospital of Basel, Switzerland, excluding only those with restenotic lesions, in need of  $\geq 4$ -mm stents and those not consenting (13). Patients presented with stable symptoms in 42%, unstable angina in 36%, and with ST-segment elevation MI in 21% of cases, whereas 69% had multivessel CAD and 66% at least 1 “off-label” indication. Patients were randomized 2:1 to DES or BMS. Follow-up findings have been reported after 18 (3) and 36 months (14). In addition, all patients surviving the initial 6 months were invited for a rest/stress myocardial perfusion scintigraphy using single-photon emission computed tomography (SPECT) (15).

This patient population and dataset provided a unique opportunity for the present prospective outcome study, the BASKET-PRO (BASKET-PROgression of CAD study). Based on a new protocol with a new ethical approval and a new written informed patient consent, all BASKET patients without clinical CAD manifestations up to 6 months after the intervention, no ischemic perfusion defects at this point in time, and surviving up to 5 years after stenting were invited to undergo a further follow-up examination including history, current therapy, clinical examination, electrocardiography as well as a second rest/stress myocardial perfusion scintigraphy performed  $5.5 \pm 0.25$  years after stent implantation. Follow-up was performed in the outpatient clinic in all patients. The patient flow is detailed in Figure 1.



**Figure 1. Patient Flow Chart**

The flow chart shows the derivation of the study population from 826 consecutive patients for the clinical follow-up and the repeat scintigraphic studies. BASKET = Basel Stent Kosten-Effektivitäts Trial; SPECT = single-photon emission computed tomography.

**Specific aims, endpoints, and definitions.** The primary aim and analysis of BASKET-PRO was to assess the magnitude of clinically relevant symptomatic and silent CAD progression remote from the stented area based on late events and perfusion findings (i.e., MI, revascularization, and new PDs in remote versus revascularized regions of the myocardium between 6 months and 5 years), irrespective of stent type. Secondary analyses evaluated the outcome between subgroups of patients treated with DES or BMS and 5-year mortality.

All events were adjudicated by a critical event committee blinded to stent type. Cardiac death was defined as death not clearly of extracardiac origin. Because death cannot be assigned to any vessel segment, death was not counted as a TV or remote event. Similarly, 2 MIs that could not be located (pre-existing left bundle branch block, unspecific electrocardiographic abnormalities) were not counted as remote or TV events. Myocardial infarction was defined as previously described (13) and attributed to myocardial segments or coronary vessels based on angiography, if available; scintigraphic findings; or serial electrocardiograms. In this study, repeat coronary angiography and revascularization were only allowed if clinically indicated. The TV was defined as the epicardial coronary artery or 1 of its side branches originally stented. In multivessel disease, all initially stented vessels were counted as target vessels. Findings were labeled non-TV or “remote” if there was clear evidence of non-TV involvement. In cases of multiple occurrences of the same event, the time to the first event was used as the time the event occurred. The period 7 months to 5 years was used to define progression of CAD. Patients with remote events and/or remote new PDs during this late period were assumed to have clinical CAD progression, whereas those without events and normal perfusion scans or no change since the first scintigraphy were not. In this study, the initial 6 months after stenting were not considered for CAD progression because early clinical assessments and scintigraphic studies for the present prospective investigation were performed at this point in time (15), which has been defined as the end of the “restenotic phase” after stenting (16).

**Myocardial perfusion studies.** SPECT studies were performed following a standard protocol (15) as previously described (17). In short, a rest-stress dual-isotope (201-thallium/99m technetium sestamibi) protocol with exercise or pharmacologic (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 from 0 = normal to 4 = no uptake. Summed stress and rest scores were calculated and converted to percentage of myocardium affected and difference scores as measures of ischemia derived thereof. Perfusion defects were correlated to TV or remote territories as recommended by the American Heart Association (18) by observers blinded to stent types used and vessels treated. A defect score that affected  $\geq 5\%$  of the myocardium was

considered significant. Silent PDs were all significant reversible defects that were not associated with anginal chest pain during the days and months prior to testing.

**Statistics.** All data are presented as mean  $\pm$  SD or proportions. Categorical variables were compared using the Fisher exact test or the McNemar test and the Student *t* test for continuous variables as appropriate. A 2-sided *p* value  $< 0.05$  was considered statistically significant. Analyses were performed using commercially available software (SPSS 19.0, SPSS, Inc., Chicago, Illinois).

## Results

Baseline characteristics of the study population (*n* = 428) are summarized in Table 1 and compared with the remaining 398 BASKET patients who were excluded here because they either had clinical events up to 6 months, had a positive or no 6-month SPECT study, or were lost to follow-up (Fig. 1). These characteristics were remarkably similar for both patient groups, the only significant difference being a higher rate of multivessel disease in excluded patients associated with early events as exclusion for this long-term evaluation (Table 1).

**Follow-up.** Five-year follow-up regarding survival was 98% and complete follow-up was reached in 97% of cases (Fig. 1). After 5 years, patients (age  $69 \pm 11$  years, 77% men) were on the following relevant drug therapy: aspirin 76%, clopidogrel 21%, both 8%, statins 64%, beta-blocking drugs 60%, calcium antagonists 15%, and long acting nitrates 3%.

Figure 1 shows that 476 patients, 64% of all BASKET patients, consented to a 6-month SPECT study and that 442 (93%) were free of symptoms, events, and ischemic PDs. Of this potential study population, 14 (3%) were lost to 5-year follow-up leaving 428 (97%) for the present long-term clinical investigation. Because 110 of them had

	Present Study Population (n = 428)	Excluded BASKET Population (n = 398)	<i>p</i> Value
Age, yrs	63.7 $\pm$ 11.2	64.0 $\pm$ 11.4	0.70
Male	77	78	0.87
Diabetes	19	19	0.93
Hyperlipidemia	77	74	0.42
Hypertension)	67	65	0.71
Smoking	29	28	0.76
Stable angina	44	40	0.25
Unstable angina	37	36	0.77
STEMI	19	24	0.08
Multivessel disease	31	42	0.001
Number of stents	1.94 $\pm$ 1.11	1.81 $\pm$ 0.97	0.06
BMS	34	34	0.83

Values are mean  $\pm$  SD or %.

BASKET= Basel Stent Kosten-Effektivitäts Trial; BMS = bare-metal stent(s); STEMI = ST-segment elevation myocardial infarction.

late follow-up events, 318 were asked for a 5-year SPECT study, of whom 206 (65%) consented. They form the basis for the long-term scintigraphic analysis.

**Long-term clinical events.** During months 7 to 60, 110 of 428 patients (25.7%) had 150 clinical events: 43 (10%) died, 36 (8.4%) suffered an MI, and 71 (16.6%) needed revascularizations for new symptoms (Table 2). Nineteen clinical events pertained at the same time to TV and remote myocardial areas (18 revascularizations and 1 MI). Event rates were lower in survivors with remote versus TV area events (9.8% vs. 14.3%,  $p = 0.019$ ), mostly due to the fact that the rate of MIs was lower in remote than in TV areas (Table 2). It is of note that 17 of 51 (33.3%) survivors with TV events underwent repeat revascularization in addition to an MI compared with only 4 of 38 (10.5%,  $p < 0.01$ ) of those with remote events. Remote MI or revascularization accounted for 46 of 124 (37.1%) of all late nonfatal events (Fig. 2), which is similar in DES- and BMS-treated patients (37.4% and 36.4%, respectively). Accordingly, there were no significant differences between DES- and BMS-treated patients in overall rates of death, MI, or revascularization (all  $p > 0.1$ , data not shown).

**New late myocardial PDs.** Compared to 6-month SPECT findings, new 5-year PDs detected 5.0 ± 0.25 years after the initial SPECT studies were noted in 48 of 206 patients (23.3%). These defects were silent in 71%, because 34 of 48 patients reported no anginal chest pain during the intermittent history. Remote PDs accounted for 18 of all 48 defects (37.5%) or 8.7% of all patients with SPECT studies (Fig. 2) (72% were asymptomatic). Remote defects were seen with similar frequency in patients with DES or BMS (9.2% vs. 7.7%,  $p = 0.8$ ).

**Late mortality.** Survival status after 5 years was known in 812 of 826 (98.3%) of the total baseline population (lost to follow-up: 2 patients early, 14 late) (Fig. 1). Overall, 115 of 812 (14.2%) patients died: 21 during the initial 6 months and 94 thereafter. Thus, mortality rate per year was one-half as high during months 7 to 60 (94 of 791 patients [21 had died before, 14 lost] or 2.64% per year) as during months 0 to 6 (21 of 824 patients [2.54%] or 5.1% per year). It is of note that cardiac causes of death after 6 months were identified in only 43 of 94 patients (45.7%). Thus, late

cardiac mortality per year was low, 1.21%, and comparable to the noncardiac mortality rate (1.43%). There were no significant differences in these mortality rates between DES- and BMS-treated patients (1.3% vs. 1.0% for cardiac and 1.5% vs. 1.2% for noncardiac mortality per year, respectively;  $p > 0.2$  each).

## Discussion

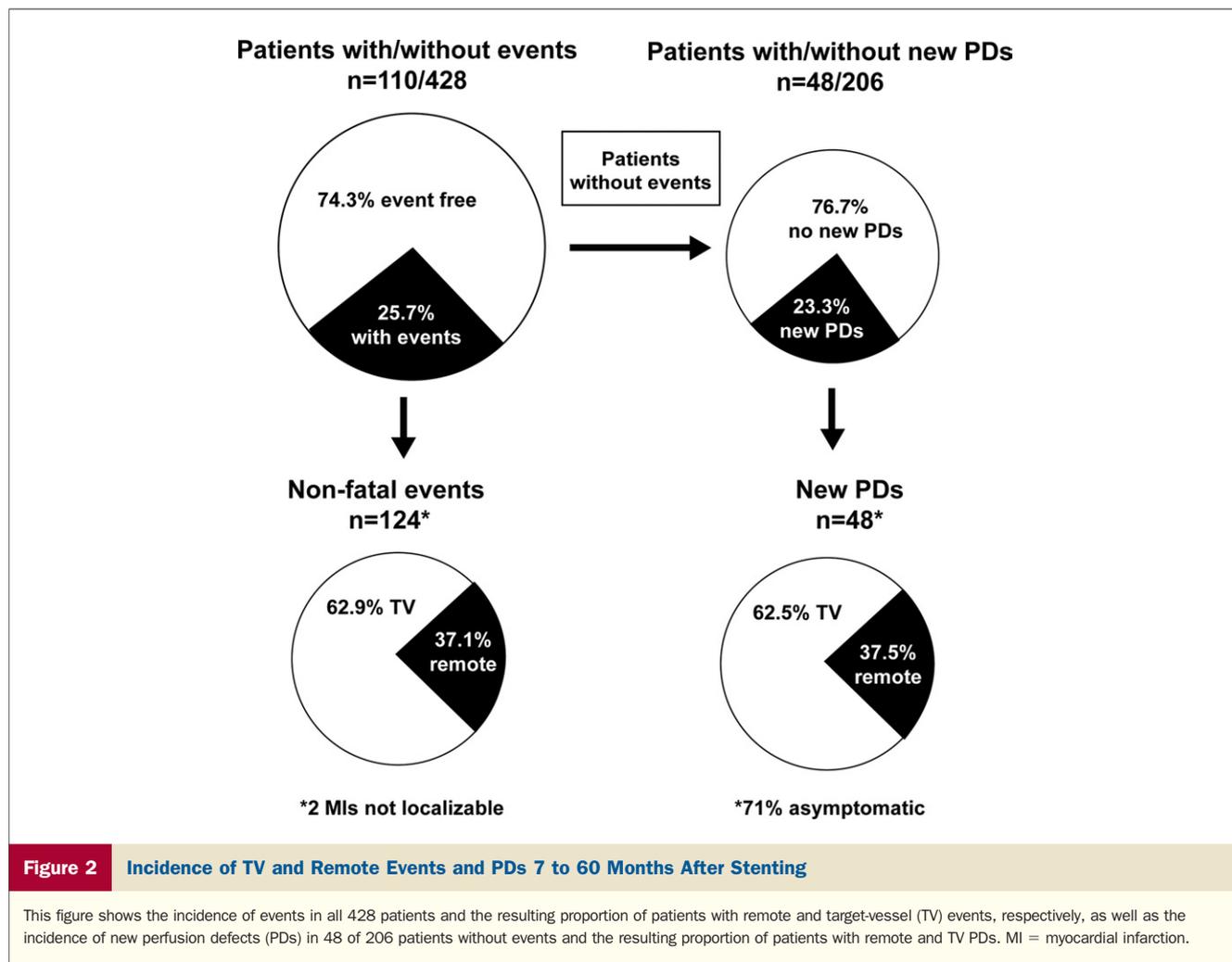
In this prospective, long-term outcome study of nonselected patients with documented successful stent implantation, TV events and/or new PDs remained more frequent than CAD progression assessed by remote events and/or new PDs even 5 years after the intervention. However, remote events accounted for almost 40% of all clinical events during these 5 years and, in addition, a similar rate of new PDs was observed in patients without follow-up events. This was similarly true for subgroups of patients randomized to DES and BMS. Progression of CAD is likely even more important than reported here because remote MIs and PDs may not only occur in remote areas but also in TVs due to disease progression proximal or distal to the stented lesion or in a side branch (19). Together with the assumption that some deaths also had a remote origin, up to one-half of all late events and/or new PDs were due to CAD progression. Progression occurred independently of stent type and manifested as acute MI, need for repeat revascularization, new PDs (which remained asymptomatic in 71%), or even death. It is important to note that during this late period after stenting, cardiac mortality rate was low (1.2% per year) and similar to noncardiac mortality (1.4% per year).

Interesting additional observations were made. The rate of late MIs was significantly higher in TV than remote areas and this was true irrespective of stent type. In addition, TV-related MIs were treated more often with revascularization, mostly acute angioplasty, than remote MIs. It is unknown whether this was due to the acute occlusion of a previously widely open artery after stenting as seen in late stent thrombosis, due to a lack of collateralization as compared to a more progressive coronary occlusion in nonpreviously treated lesions or to other unknown patient factors. The possibility of underlying late stent thrombosis

**Table 2 TV Versus Remote Clinical Events During Months 7 to 60**

		Overall (n = 428)	Overall (n = 428)		DES (n = 284)		BMS (n = 144)	
			TV	Remote	TV	Remote	TV	Remote
Death	n	43 (10)	—	—	—	—	—	—
MI*	n	36 (8.4)	27 (6.3)	8 (1.9)	21 (7.4)	7 (2.5)	6 (4.2)	1 (0.125)
	p Value			0.002		0.011		0.125
Revascularization†	n	71 (16.6)	51 (11.9)	38 (8.9)	36 (12.7)	27 (9.5)	15 (10.4)	11 (7.6)
	p Value			0.1		0.2		0.424
Patients with any events‡	n	110 (25.7)	61 (14.3)	42 (9.8)	45 (15.8)	30 (10.6)	16 (11.1)	12 (8.3)
	p Value			0.019		0.037		0.424

Values are n (%). \*Two MIs could not be attributed to TV or remote areas (see Methods): 1 MI was a TV and remote area MI. †Eighteen revascularizations were done at the same time in TV and remote vessels. ‡The first column includes death; the other columns do not include death. Some patients had >1 event.  
BMS = bare-metal stent(s); DES = drug-eluting stent(s); MI = myocardial infarction; TV = target vessel.



has been postulated previously during the second and third years after stent implantation (3,14) and has been noted in this study in two-thirds of patients with MI, which is not significantly more often in DES- versus BMS-treated patients. However, findings of a recent trial suggested that late stent thrombosis may be less of a clinical issue with the use of newer DES and current medical management, at least in large coronary arteries (20).

**The “natural history” of CAD in prior stent studies.** The “natural history” of CAD is a moving target because it reflects disease progression, as well as the effects of drug and revascularization therapies, secondary prevention, and life style modification. The sum of these measures has been associated with a significant decrease in overall mortality (21). Revascularization by angioplasty and stenting contributed to this effect in patients with acute CAD (22,23), but it did not reduce mortality in patients with chronic disease (24,25). However, revascularization reduced ischemic symptoms consistently during the initial year of therapy (25). Later on, this group difference disappeared due to many medical patients needing revascularization for refractory symptoms and the fact that long-term outcome is deter-

mined largely by disease progression as shown in a low-risk clinical trial population after stenting (10).

Two prior studies addressing non-TV events in DES versus BMS patients (11,12) had notable limitations. One reported observations of pooled TAXUS trials with incomplete follow-up rates, difficulties in adjudication of late events, and inclusion of patients with uncomplicated lesions only as acknowledged limitations (11). The other study based on the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesion) trial (12) also examined low-risk patients with incomplete 5-year follow-up. The lack of mortality data in 15% of patients and the likelihood that spontaneous late MIs were missed were important limitations here. In addition, all deaths were counted as TV as well as non-TV events, making comparisons of remote versus TV event rates even more difficult. In both studies, outcomes were influenced by protocol-mandated follow-up angiographies. Another recent study on the natural history of CAD in a stent patient population showed that cardiovascular events during 3 years of follow-up were similarly attributable to recurrence at culprit-lesion and non-culprit-lesion sites defined by baseline angiography (26). In contrast

to these reports, the present study highlights the clinical relevance of CAD progression after revascularization with stent implantation. It is unique in that it included only patients with successful, complete revascularization documented 6 months after stent implantation (important in unselected multivessel CAD patients), had an almost complete clinical 5-year follow-up (98%), and incorporated serial SPECT studies performed in two-thirds of all patients without follow-up events, allowing for the first time not only to evaluate late cardiovascular events but also symptomatic and silent ischemia. Together, the prevalence of clinically relevant CAD progression was much higher than previously reported (11,12,26), about double that observed based on clinical events alone, and this was true independently of stent type used, in patients randomized to DES versus BMS.

**Role of serial scintigraphic testing.** Myocardial perfusion scintigraphy is a well-established method to detect serial changes of myocardial perfusion after revascularization (27) and after drug therapy (28). Findings of the present study, the hitherto longest serial myocardial perfusion scintigraphic study covering a 5-year period, were consistent with results of remote versus TV clinical events, reinforcing those findings and demonstrating that CAD progression may often manifest late as silent ischemia, if searched for.

**Study limitations.** The present study has several limitations. About one-third of patients without events did not consent to a second SPECT study. Deaths could not be attributed to any coronary vessel (as in reference 26). Target-vessel events and PDs could have occurred due to coronary obstructions remote from the stent (discussed earlier) and the scintigraphic method detects "clinically relevant" PDs but may underestimate CAD progression. These facts limit a precise assessment of the magnitude of CAD progression. This could only be achieved with repeat coronary angiographies in all patients, an ethically questionable endeavor using an invasive diagnostic test. However, based on the scintigraphic findings, the present study suggests that the prevalence of CAD progression is at least double that reported from clinical events alone. Then, in view of relatively low numbers of patients, comparisons of subgroups with DES versus BMS should only be done with great caution in this trial, particularly relating to low-frequency events such as stent thrombosis. Finally, these results relate to first-generation DES, but because non-TV event rates did not differ between stent types, results of CAD progression may hold true also for future generations of stents.

## Conclusions

The observation of BASKET-PRO that CAD progression 5 years after successful stent implantation is more prevalent than previously assumed and independent of stent type has important implications. The fact that close to 40% of all late events and almost 40% of all new PDs in patients without events were detected in areas remote from stents highlights the importance of CAD progression and, thus, for long-

term secondary prevention after revascularization. It stresses the need to differentiate remote from stent-related TV events and/or new PDs in long-term stent safety studies. In addition, the high rate of silent CAD progression raises the question whether or not all patients should undergo ischemia-testing several years after stent implantation.

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