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Pedersen, S.S.; Lemos, P.A.; van Vooren, P.R.; Liu, T.K.; Damen, J.; Erdman, R.A.M.; Serruys, P.W.; van Domburg, R.T.

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Type D Personality Predicts Death or Myocardial Infarction After Bare Metal Stent or Sirolimus-Eluting Stent Implantation

A Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) Registry Substudy

Susanne S. Pedersen, PHD,*‡ Pedro A. Lemos, MD,* Priya R. van Vooren,* Tommy K. K. Liu,* Joost Daemen,* Ruud A. M. Erdman, PHD,*† Pieter C. Smits, MD, PHD,* Patrick W. J. C. Serruys, MD, PHD, FESC, FACC,* Ron T. van Domburg, PHD*

Rotterdam and Tilburg, The Netherlands

OBJECTIVES We investigated the effect of Type D personality on the occurrence of adverse events at nine months in patients with ischemic heart disease (IHD) after percutaneous coronary intervention (PCI) with sirolimus-eluting stents (SESs) or bare stents. Type D patients experience increased negative emotions and tend not to express these emotions in social interactions.

BACKGROUND The SES is a new advent in interventional cardiology that reduces the restenosis rate and the risk of a major adverse cardiac event, but the SES has not been shown to confer any benefits on death or myocardial infarction (MI).

METHODS Consecutive patients with IHD (n = 875) enrolled in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry completed the Type D Personality Scale (DS14) six months after PCI. The end point was a composite of death and MI. Events occurring before administration of the DS14 were excluded from analyses.

RESULTS At nine months' follow-up, there were 20 events. Type D patients were at a cumulative increased risk of adverse outcome compared with non-Type D patients: 5.6% versus 1.3% ($p < 0.002$). Type D personality (odds ratio [OR] 5.31; 95% confidence interval [CI] 2.06 to 13.66) remained an independent predictor of adverse outcome adjusting for all other variables, including SES versus bare-stent implantation.

CONCLUSIONS Type D personality was an independent predictor of adverse events in patients optimally treated with the latest advent in interventional cardiology. The DS14 could be used as a screening instrument in routine clinical practice to optimize risk stratification in IHD patients. (J Am Coll Cardiol 2004;44:997–1001) © 2004 by the American College of Cardiology Foundation

The effectiveness of percutaneous coronary intervention (PCI) in patients with ischemic heart disease (IHD) has improved considerably since the procedure was first introduced in the late 1970s (1). Nevertheless, in-stent restenosis has remained as the major limitation hampering the clinical efficacy of percutaneous revascularization. With the introduction of drug-eluting stents, the incidence of restenosis has decreased significantly compared with conventional stenting, reducing the need for repeat revascularization ranging from 59% and higher in selected patients (2,3). Drug-eluting stents have not been shown to decrease the incidence of death or myocardial infarction (MI), and in this new "restenosis-free" era following PCI, therefore, there is still a need to identify subgroups at increased risk of death or MI. This may warrant the examination of nontraditional risk factors, such as psychological risk factors, in addition to the established biomedical risk factors.

From the pre-drug-eluting stent era, there is evidence to suggest that emotionally distressed patients comprise one subgroup that does not benefit optimally after cardiac invasive treatment. Depression has been associated with a more than two-fold increased risk of a recurrent cardiac event after coronary artery bypass graft surgery (CABG) (4,5). Prior history of depression and vital exhaustion have been shown to lead to adverse clinical outcomes in patients after PCI (6,7).

Patients with a Type D or distressed personality form another subgroup that is at risk of inadequate response to treatment. Type D personality has been shown to independently predict adverse clinical outcome in IHD, and the prognostic power of the Type D personality equals that of left ventricular dysfunction (8–10). Type D personality defines individuals who experience increased negative emotions and who do not express these emotions in social

From the Departments of *Cardiology and †Medical Psychology and Psychotherapy, Thoraxcenter, Erasmus Medical Center, Rotterdam, The Netherlands; and ‡Department of Psychology and Health, Tilburg University, Tilburg, The Netherlands. This study was supported by the Erasmus Medical Center, Rotterdam, The Netherlands, and by Cordis, a Johnson & Johnson Company, Miami Lakes, Florida.

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
CABG	= coronary artery bypass graft surgery
CI	= confidence interval
CK	= creatine kinase
IHD	= ischemic heart disease
MI	= myocardial infarction
NA	= negative affectivity
OR	= odds ratio
PCI	= percutaneous coronary intervention
RESEARCH	= Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital registry
SES	= sirolimus-eluting stent
SI	= social inhibition
TIMI	= Thrombolysis In Myocardial Infarction
TNF	= tumor necrosis factor

interactions (9). To date, no study has investigated the impact of Type D personality on the prognosis of patients treated with PCI in the drug-eluting stent era.

The objective of this study was to investigate the impact of Type D personality on prognosis at nine months' follow-up in consecutive unselected IHD patients treated with either sirolimus-eluting stents (SESs) or bare stents.

METHODS

Study design and patient population. Since April 2002, the SES (Cypher; Johnson & Johnson–Cordis unit, Cordis Europa NV, Roden, The Netherlands) has been utilized as the device of choice for all patients treated with PCI in our institution, as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry (11,12). The study protocol of this registry has been described elsewhere (12). Briefly, it is a single-center study that evaluates the impact of unrestricted SES implantation on the clinical outcomes of patients treated in the "real world" of interventional cardiology. To accomplish this objective, all patients treated with PCI were considered for enrollment regardless of anatomical or clinical presentation. For comparison, a control group was composed of all consecutive patients treated with conventional percutaneous techniques in the period immediately before the introduction of the SES.

In both study phases, patients were prospectively followed up for clinical adverse events. Additionally, all living patients were contacted at six months to complete a questionnaire that evaluates the presence of Type D personality. Between October 2001 and October 2002 (six-month enrollment in each study phase), a total of 1,237 patients were treated with pure bare stents or pure SES; of these, 875 patients (71%) (SES: n = 358; bare stents: n = 517) returned the questionnaire.

Nonresponders were younger and more likely to have had a previous MI, to suffer from diabetes, or to be treated with angiotensin-converting enzyme (ACE) inhibitors. They were less likely to suffer from renal impairment or to be treated with aspirin and beta-blockers ($p < 0.05$). No other statistically significant differences were found between responders and nonresponders on baseline characteristics. Ethical approval was obtained from the hospital ethics committee, and the study was carried out in accordance with the Helsinki Declaration. Every patient provided written, informed consent.

Interventional procedure. All interventions were performed according to current standard guidelines, and the final interventional strategy was entirely left to the discretion of the operator, aiming at a final residual stenosis <30% in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. Periprocedural adjunctive medications were used according to the operator's decision. All patients were advised to maintain lifelong aspirin therapy. One-month clopidogrel treatment (75 mg/day) was recommended for patients treated in the pre-sirolimus phase. For patients treated with SES, clopidogrel was prescribed for three months, unless one of the following was present (in which case clopidogrel was maintained for at least six months): multiple SES implantation (>3 stents), total stented length >36 mm, chronic total occlusion, bifurcations, or treatment of in-stent restenosis.

Materials. Sociodemographic variables included gender and age. Information on clinical variables (previous MI, previous CABG, previous PCI, multivessel disease, hypertension, hypercholesterolemia, diabetes mellitus, renal impairment, and smoking status) was sampled from the medical records.

Type D personality was assessed with the 14-item Type D Personality Scale (DS14) (13). Type D personality characterizes those who tend to experience increased negative emotions and who do not express these emotions in social interactions. The DS14 consists of the subscales negative affectivity (NA) (e.g., "I often feel unhappy") and social inhibition (SI) (e.g., "I am a 'closed' person"). A score ≥10 on both subscales denotes those with a Type D personality (13). The DS14 has adequate reliability with Cronbach's alpha = 0.88/0.86 and test-retest reliability r = 0.72/0.82 for the NA and the SI subscales, respectively (13). The validity of the subscales has been confirmed against scales measuring similar constructs (13). The DS14 was administered to patients six months after PCI for logistic reasons. However, Type D personality has been shown to exert a stable influence on outcome after invasive and medical treatment compared with, for example, gender (14).

Clinical end point and definitions. The primary end point was the occurrence of combined death (all-cause) or nonfatal MI during the nine months of follow-up. Myocardial infarction was diagnosed by a rise in the creatine kinase (CK) level to more than twice the upper normal limit with an increased CK MB. Deaths (SES = 14; bare = 22) occurring before the administration of the DS14 were excluded from statistical analyses whereas MIs were included as prior MIs.

Statistical analysis. Discrete variables were compared with the chi-square test and are presented as numbers and percentages. Continuous variables were compared with the Student *t*-test and are presented as means ± SD. The cumulative incidence of death/MI was estimated according to the Kaplan-Meier method. Differences between Type D versus non-Type D personality on outcome were compared with the log-rank test. The zero time point indicates the time of administration of the DS14 and will be referred to as baseline in the remainder of this paper. Univariate and multivariate logistic regression analyses were used to examine the influence of demographics (gender and age), clinical variables (previous MI, previous CABG, previous PCI, multivessel disease, hypertension, hypercholesterolemia, diabetes mellitus, renal impairment, and smoking status), stent type (SES vs. bare), and personality type (Type D vs. non-Type D) on death/MI. The multivariate analyses were conducted in two steps. In the first step, all clinical variables were entered in a multivariate model and only those that were significant at $p < 0.05$ were entered in the second step together with gender, age, stent type, Type D personality, and the interaction term stent type × personality type. All statistical tests were two-tailed. A value of $p < 0.05$ was used for all tests to indicate statistical significance. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported. All statistical analyses were performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois).

RESULTS

Patients with Type D personality were more likely to smoke compared with patients without Type D personality (37% vs. 29%, $p = 0.01$). No other statistically significant differences were found between the two groups on baseline characteristics (Table 1). We also found no statistically significant differences between patients with or without Type D personality on treatment with beta-blockers, calcium antagonists, nitrates, ACE inhibitors, statins, aspirin, or clopidogrel ($p > 0.05$).

At nine months' follow-up, there were 20 events, i.e., 9 deaths and 11 MIs.

Risk of a composite of death and MI. In a pooled sample of patients regardless of stent type, patients with Type D personality were at a cumulative increased risk of a composite of death and MI at nine months compared with patients without Type D personality: 5.6% versus 1.3% (OR = 4.73; 95% CI 1.87 to 12.00) (Fig. 1). Previous CABG (OR = 3.43) was also associated with an increased risk of death or MI in univariate analyses (Table 2).

Independent predictors of outcome. In a multivariate model containing all clinical and demographic variables, previous CABG (OR = 4.00; 95% CI 1.25 to 12.78) was the only variable that was significantly related to death or MI. Previous CABG was subsequently entered into a multivariate model together with Type D personality, gender, age, stent type (SES vs. bare), and the interaction term stent type × personality type. Type D personality (OR = 5.31; 95% CI 2.06 to 13.66) remained an independent predictor of the incidence of death or MI adjusting for all other variables. Previous CABG (OR = 3.03; 95% CI 1.04 to 8.87) was also associated with an increased risk of death or MI. No association was found between stent type and this end point ($p = 0.42$), nor was the interaction term stent type × personality type statistically significant ($p = 0.11$).

Table 1. Baseline Characteristics (Six Months After PCI)

	Type D (n = 254) n (%)	Non-Type D (n = 621) n (%)	p Value
Demographic factors			
Female gender	77 (30)	169 (27)	0.35
Age, mean (SD)	61 (12)	63 (11)	0.07
Stent type			
SES	106 (42)	252 (41)	0.75
Clinical			
Previous MI*	98 (39)	229 (37)	0.64
Previous CABG	28 (11)	73 (12)	0.76
Previous PCI	66 (26)	153 (25)	0.68
Multivessel disease	135 (53)	323 (52)	0.76
Hypertension†	104 (41)	235 (38)	0.39
Hypercholesterolemia‡	214 (84)	495 (80)	0.12
Diabetes mellitus†	43 (17)	84 (14)	0.20
Renal impairment§	83 (33)	182 (30)	0.37
Current smoking‖	95 (37)	178 (29)	0.01

*Based on the judgment of the treating physician. †Present if being treated for the condition. ‡Total cholesterol levels >240 mg/dl or on lipid-lowering medication. §Indicated by creatinine clearance <60 ml/min. ‖Based on self-report.

CABG = coronary artery bypass surgery prior to index event; MI = myocardial infarction; PCI = percutaneous coronary intervention prior to index event; SES = sirolimus-eluting stent.

DISCUSSION

This is the first study to investigate the influence of psychological risk factors on cardiac prognosis in post-PCI patients in the new drug-eluting stent era. Type D personality significantly increased the nine-month incidence of death or MI in patients treated with PCI. Type D personality was shown to influence outcomes regardless of the stent type used, i.e., conventional bare stents or last-generation SES, and established biomedical risk factors. It is

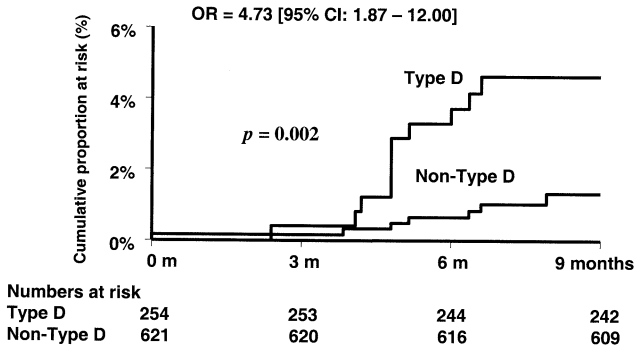

Figure 1. Nine months' cumulative risk of death or myocardial infarction after percutaneous coronary intervention by personality type. OR = odds ratio; CI = confidence interval.

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Table 2. Predictors of Adverse Events at Nine Months (Univariate Analysis)

	Death/MI (n = 20)		
	OR	(95% CI)	p Value
Psychological risk factors			
Type D personality	4.73	(1.87–12.00)	0.001
Demographic factors			
Female gender	3.59	(0.83–15.59)	0.09
Age, mean (SD)	1.02	(0.98–1.06)	0.38
Stent type			
SES	1.46	(0.60–3.54)	0.41
Clinical risk factors			
Previous MI*	1.70	(0.70–4.12)	0.24
Previous CABG	3.43	(1.29–9.13)	0.01
Previous PCI	1.63	(0.64–4.15)	0.32
Multi-vessel disease	1.12	(0.46–2.72)	0.81
Hypertension†	0.85	(0.34–2.15)	0.73
Hypercholesterolemia‡	0.54	(0.20–1.42)	0.21
Diabetes mellitus†	1.49	(0.49–4.52)	0.48
Renal impairment§	0.75	(0.27–2.09)	0.58
Smoking‖	1.19	(0.47–3.02)	0.71

*Based on the judgment of the treating physician. †Present if being treated for the condition. ‡Total cholesterol levels >240 mg/dl or on lipid-lowering medication. §Indicated by creatinine clearance <60 ml/min. ‖Based on self-report.
CI = confidence interval; OR = odds ratio. Other abbreviations as in Table 1.

noteworthy that the risk associated with Type D personality was on par with that of traditional biomedical risk factors.

Given the success of drug-eluting stents in reducing restenosis, it seems timely to shift focus toward the identification of subgroups of patients at increased risk of mortality. This may warrant expanding our focus to include more nonconventional risk factors, such as psychological factors. Previous studies in patients following CABG have shown that depression was associated with a more than two-fold increased risk of adverse outcome (4,5). In the pre-drug-eluting stent era, prior history of depression and vital exhaustion have been shown to moderate the effects of PCI on outcome (6,7). In the current study, we found that Type D personality was an independent predictor of death or MI. This finding concurs with those of previous 5- to 10-year follow-up studies in the pre-drug-eluting stent era on Type D personality (8–10). Surprisingly, however, in the current study, Type D personality was related to adverse outcome already at nine months. Taken together, these results indicate that subgroups of cardiac patients with a particular psychological profile may not respond adequately to treatment, and that for these subgroups some form of psychosocial intervention is warranted.

Personality is considered to exert a stable influence on behavior, but this does not necessarily mean that the level of distress of patients with a Type D personality cannot be modified. However, psychosocial intervention studies targeting negative emotions to decrease the risk of adverse cardiovascular events have yielded mixed findings (15–18). The extent to which patients with Type D personality may experience benefits from behavioral treatment needs to be examined in future intervention trials.

In the future, it also will be important to elucidate which pathophysiological mechanisms are responsible for the adverse effect of Type D personality on cardiac prognosis. Preliminary evidence in patients with chronic heart failure suggests that patients with Type D personality may have increased levels of tumor necrosis factor (TNF)-alpha and soluble TNF-alpha receptors compared with patients without Type D personality (19). These cytokines have been associated with the pathogenesis and poor prognosis of heart failure (20). In a study of healthy undergraduates, the SI and NA components of Type D personality were associated with heightened blood pressure reactivity and greater cortisol reactivity to stress (21). Further research into the mechanisms responsible for the link between Type D personality and cardiac prognosis is warranted in order to optimize treatment strategies.

The results of the current study should be interpreted with some caution. We had no information on left ventricular dysfunction and New York Heart Association (NYHA) functional classification, which are known prognostic indicators. Because of logistic reasons, the DS14 was administered six months after PCI. This may have biased our results, as patients who died between zero and six months did not have the opportunity to complete the DS14. On the other hand, Type D personality has been shown to exert a stable effect on outcome after invasive and conservative treatment (14). Treatment type (SES vs. bare stent) was not randomized given that implantation with SES has been adopted as the treatment of choice for all PCI patients referred to our institution. However, patients were representative of the "real world" of interventional cardiology, as no exclusion criteria were applied.

In summary, Type D personality was identified as an independent predictor of adverse cardiac outcome in patients treated optimally with the latest advent in interventional cardiology. The risk associated with Type D personality was similar to that of traditional cardiovascular risk factors. The DS14 could be used as a screening instrument in routine clinical practice to optimize risk stratification in patients with IHD. The scale is a valid and brief instrument that constitutes little burden to patients and to clinical practice.

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Reprint requests and correspondence: Dr. Susanne S. Pedersen, Department of Psychology and Health, Tilburg University, Room P503a, Warandelaan 2, 5000 LE Tilburg, The Netherlands. E-mail: s.s.pedersen@uvt.nl.

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