Personality as Independent Predictor of Long-Term Mortality in Patients With Coronary Heart Disease

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Summary

Emotional distress has been related to mortality in patients with coronary heart disease (CHD), but little is known about the role of personality in long-term prognosis. We hypothesized that type-D personality, i.e. the tendency to suppress emotional distress, was a predictor of long-term mortality in CHD, independent of established biomedical risk factors.

Subjects were 268 men and 35 women with angiographically documented CHD, aged 31 to 79 years, who participated in an outpatient rehabilitation program. All patients filled out personality questionnaires at entry in the program and were contacted after 6 to 10 years (M = 7.9) to determine survival status. The main end point was death from all causes.

At follow-up, 38 patients had died; there were 24 cardiac deaths. Rate of death was 27% (23 out of 85) for type-D patients versus 7% (15 out of 218) for patients without type-D, $p<0.00001$. The association between type-D personality and mortality was still evident more than 5 years after the coronary event and was found in both men and women. Mortality was also associated with impaired left ventricular function, 3-vessel disease, low exercise tolerance, and no thrombolytic therapy. After we controlled for these biomedical predictors in multiple logistic regression analysis, the impact of type-D remained significant (odds ratio 4.1; 95% CI, 1.9 to 8.8; $p=0.0004$). In this group of CHD patients, type-D was an independent predictor for both cardiac and noncardiac mortality. Social alienation and depression were also related to mortality, but did not add to the predictive power of type-D.

Type-D personality was a significant predictor of long-term mortality in patients with established CHD, independent of biomedical risk factors. Personality traits should be accounted for in the association between emotional distress and mortality in CHD.

Key words coronary heart disease ● personality ● social alienation ● depression ● prognosis

Introduction

Biomedical research on the prognosis and treatment of patients with coronary heart disease (CHD) has identified several important prognostic factors [1-3]. Apart from these biomedical factors, it has been suggested that there seems to be a relation between personality and CHD [4]. Evidence indicates that psychosocial factors may affect longevity [5], and particular factors such as social alienation [6-9] and depression [10,11] have been associated with a poor prognosis in patients who survived a myocardial infarction (MI). However, little is known about the role of personality factors in prognosis in patients with CHD and about the prognostic value of psychosocial stress more than 5 years after the coronary event.

We therefore examined the role of personality in 6-10 year mortality in CHD patients, controlling for biomedical prognostic factors such as the severity of cardiac disease. This study focused on the tendency to inhibit self-expression in social interaction, i.e. social inhibition [12] and the tendency to experience negative emotions, i.e. negative affectivity [13] because these personality traits may promote social alienation and depression [e.g., 14]. The follow-up of most studies is 0.5 to 5 years (mean= 2.1 years) [6-11]; hence, long-term studies on the prognostic role of psychosocial stress in patients with CHD are still lacking.

Methods

Subjects

Two hundred sixty eight men and 35 women, aged 31-79 years (M=55.4 years, SD 7.9), were selected from a consecutive series of CHD patients who were enrolled in the Antwerp cardiac rehabilitation program between January 1985 and December 1988. Patients were eligible for this study if they had experienced a recent coronary event within 2 months before entry into the program. There were 182 patients with a recent MI and 121 coronary patients without recent MI

who underwent coronary bypass surgery or angioplasty (CABG/PTCA). Patients with a previous myocardial infarction or impaired left ventricular function were included. Exclusion criteria were the presence of another serious disease at baseline, (e.g., renal failure, cancer) and no assessment of left ventricular ejection fraction at baseline.

All patients underwent a standardized treatment regimen -i.e., an outpatient rehabilitation program comprising 36 sessions of ECG-monitored aerobic exercise training and 6 psychosocial counseling sessions in groups of patients and spouses. Individual medical and psychological counseling tailored the rehabilitation program to the needs of each patient. The presence of patients in the Antwerp rehabilitation program is not a function of severity of cardiac disorder, but largely reflects the attitude of referring physicians towards cardiac rehabilitation. Standard medical care in the follow-up interval was similar for all patients, and basically consisted of a routine cardiologic check-up every six months. Women were included in the present study because cardiac mortality after MI is independent of gender [15] and preliminary evidence suggests that psychosocial factors may be related to long-term mortality in women with premature MI [16]. A subset of 93 patients also participated in a pilot study on the relation between personality and 2-5 year mortality [17].

Type-D Personality

The present study was preceded by a number of psychological studies defining distinctly different personality types in patients with CHD [17-19]. Personality types can be delineated either through empirical induction (relying on statistical procedures) or through theoretical deduction (relying on specific assumptions). As previously described, we used a combined inductive-deductive approach to analyze the role of personality in the context of CHD [18].

For this purpose, we initially used cluster analysis; i.e., a multivariate statistical procedure that is specifically designed to classify subjects into homogeneous subtypes. This inductive approach

yielded a discrete personality type of CHD patients that was characterized by high scores on both negative affectivity and social inhibition [19]. External measures that were not involved in the clustering indicated that these patients were high in emotional distress and low in subjective well-being. The reliability of this personality type was demonstrated across parallel data sets, and follow-up assessment indicated that these patients still experienced substantial distress at 15 months after the initial assessment [19].

TABLE 1 On the basis of this empirically generated model, a subsequent study [17] used a deductive approach to define the distressed personality type or type-D in patients with CHD (Table 1). By analogy with cluster analysis, a median split on measures of negative affectivity and social inhibition was used as a definition of type-D; i.e. patients with type-D tend simultaneously to experience negative emotions (as indicated by a negative affectivity score > median) and inhibit self-expression (as indicated by a social inhibition score > median). As a result, type-D is characterized by the chronic suppression of negative emotions across time and situations. Preliminary findings suggested that type-D, in fact, was associated with depression, social alienation, and 2 to 5 year mortality in middle-aged men who survived a MI [17].

Accordingly, the definition of type-D was derived before the mortality outcome was known in the present study. In this study, we hypothesized that type-D was an independent predictor of long-term mortality in CHD. First, inhibiting emotional expression may promote disease [20]. Suppressed anger, for example, has been associated with hypertension [21], incidence of CHD [22] and mortality [23]. Second, type-D patients are prone to depression and social alienation, two psychosocial factors that may increase mortality in CHD [6-11].

As described previously [17], a median split on the "trait" scale of the State-Trait Anxiety Inventory [24] and the "social inhibition" scale of the Heart Patients Psychological Questionnaire [25] was used to classify 85 patients as type-D (i.e., "trait-anxiety" $\geq$ 43 and "social inhibition" $\geq$ 12) and 218 patients as not type-D. Among patients with CHD, these scales are valid measures

of negative affectivity and social inhibition, respectively [13,19].

Prognostic Factors

The status of left ventricular function and the extent of coronary obstructive disease are two indices of disease severity that are powerful predictors of mortality for CHD patients [3]. These indices were included in our study to ensure that any observed personality effects were independent of disease severity. An impaired left ventricular function was defined as a left ventricular ejection fraction (LVEF) ≤40% as calculated from ventricular angiography and a great extent of coronary disease as three vessels with ≥70% reduction in internal diameter.

Biomedical risk assessment also included noninvasive measurement and clinical data [1-3]. Clinical risk factors included older age (i.e., ≥56 years), history of MI, one or more previous MIs, anterior location of MI, no thrombolysis after MI, no aspirin therapy or no â-blocker therapy at discharge from the rehabilitation program, poor compliance with the exercise regimen, failure to quit smoking, and history of hyperlipidemia. A poor exercise tolerance was defined by a median split for peak work load on a symptom-limited exercise test 6 weeks after the coronary event (i.e., ≤140 and ≤120 Watt for younger and older men; ≤100 and ≤80 Watt for younger and older women, respectively). The frequency of angiography and CABG/PTCA in the follow-up interval was also recorded in this study.

Social alienation and depression were measured by the Millon Behavioral Health Inventory (MBHI) [26] in the present study to examine the hypothesis that type-D may explain the association between these particular psychosocial factors and mortality in CHD patients [6-11]. The "social alienation" scale of the MBHI measures perception of lack of social support. Patients were classified as being prone to social alienation if they scored above the median of this scale (i.e., ≥7). The "premorbid pessimism" and "future despair" scales of the MBHI measure

cognitive dimensions of depression. Patients were classified as being prone to depression if they scored above the median of both scales (i.e., ≥10 and ≥12, respectively). In addition, use of benzodiazepines was conceptualized as a non-test marker of emotional distress. Use of benzodiazepines has been related to a poor prognosis in MI patients [17,27].

Procedure

At entry in the rehabilitation program, all patients filled out psychological questionnaires. The psychological status of chronically ill patients represents not the demands of their medical condition but rather reflects enduring personality traits [28]. Research also indicates that depression [29] and the association between depression and mortality [10,11] are independent of disease severity in MI patients. Accordingly, type-D was not associated with disease severity in this study: type-D patients with a recent MI did not differ from non-type-D MI patients in LVEF (51% vs 55%,p=0.10) or three-vessel disease (29% vs 27%,p=0.71); type-D patients with a recent CABG or PTCA did not differ from their non-type-D counterparts in LVEF (60% vs 64%,p=0.10) or three-vessel disease (65% vs 60%,p=0.62). Therefore, personality assessment after the occurrence of a coronary event was warranted.

The follow-up interval, as determined retrospectively by the timing of the initial assess-ment, varied between 6 and 10 years (mean= 7.9). Between September and December 1994, subjects and their families were contacted to determine survival status. The main end point in this study was death from all causes. In secondary analyses, causes of death were divided into cardiac and noncardiac categories [30]. Mortality data were derived from hospital records and the patient's attending physician was always involved in the classification of cause of death.

Statistical Analysis

We initially stratified patients by covariates of CHD severity to examine the effect of type-D on the risk for death within risk strata. Next, we conducted univariate analyses after stratifying

patients by time of death (> 5 years after coronary event), cause of death and gender. Differences in biomedical and psychosocial characteristics according to vital status were analyzed for total, cardiac and noncardiac mortality. Dichotomous variables were analyzed using Chi-square and Fisher's exact test; continuous variables using unpaired t-test.

To determine the prognostic value of type-D in addition to biomedical and psychosocial prognostic factors, we conducted a number of multivariate analyses using multiple logistic regression analysis [31]. Criteria for entry and removal were based on the likelihood ratio test with entry and remove limits set at $p \leq 0.10$ and $p \geq 0.10$. Multivariate analyses were carried out again with cardiac death and noncardiac death as an endpoint, respectively. Patients were also stratified by exercise tolerance and personality type to examine the effect of a poor physical and mental health on the risk for death. Chi-square test was used for this purpose.

Results

There were no patients lost to follow-up. After 6-10 years of follow-up, 38 of 303 patients (14%) had died; there were 24 (63%) cardiac and 14 (37%) noncardiac deaths. All deaths were attributable to natural causes; there were no violent deaths caused by accident, homicide, or suicide. There was no significant difference in mortality among men and women ($p=0.26$) or among MI and CABG/PTCA patients ($p=0.77$). Hence, pooling of subjects in one category of coronary patients in further statistical analyses could be justified.

Personality was significantly associated with an increased risk for death. Type-D patients had nearly four times the risk for death compared with patients with another personality; i.e., 27% mortality (23 deaths out of 85) versus 7% mortality (15 deaths out of 218), $p<0.00001$. After deleting the 93 subjects of the pilot study [17] in the analysis, type-D patients still had four times the risk for death compared with patients with another personality; i.e., 21% mortality (13 deaths out of 61) versus 5% mortality (8 deaths out of 149), $p=0.0005$.

FIGURE 1 This personality effect was not accounted for by the severity of cardiac disease: the association between type-D personality and mortality remained significant after adjustment for left ventricular function and extent of coronary obstructive disease, respectively (Figure 1). There were 14 deaths that occurred more than 5 years after the coronary event. Type-D patients had three times the risk for death after more than 5 years as compared to patients without type-D; i.e., 7 deaths out of 69 (10%) versus 7 deaths out of 210 (3%), p=0.032.

Type-D was associated with mortality in both men (18 of 71=25% versus 14 of 197=7%, p=0.00005) and women (5 of 14=36% versus 1 of 21=5%, p=0.028), and was associated with cardiac death (15 of 77=20% versus 9 of 212=4%, p=0.00003) as well as noncardiac death (8 of 70=11% versus 6 of 209=3%, p=0.009). Rate of death for patients scoring high on trait-anxiety but low on social inhibition (4 of 66= 6%) was smaller than that for type-D patients (p=0.0008) and did not differ from that for patients scoring low on trait-anxiety (11 of 152= 7%), p=0.75. Likewise, rate of death for patients scoring high on social inhibition but low on trait-anxiety (5 of 81= 6%) was smaller than that for type-D patients (p=0.0003) and did not differ from that for patients scoring low on social inhibition (10 of 137= 7%), p=0.75. Accordingly, it was not trait-anxiety or social inhibition per se but rather the interaction of trait-anxiety with social inhibition that was predictive of mortality.

TABLE 2 Patients who died also differed from survivors in several biomedical and psychosocial characteristics that have been related to mortality in coronary patients by others (Table 2). They were more likely to have a LVEF≤40%, three-vessel disease, a poor exercise tolerance, previous MIs, complaints of social alienation, depressive symptoms, benzodiazepine-abuse, and were marginally less likely to have been treated with thrombolysis and marginally less likely to adhere to the exercise regimen. Cardiac death was associated with type-D personality (p<0.0001), poor exercise tolerance (p<0.001), LVEF ≤40%, three-vessel disease, previous MI, depression

($p<0.01$), history of MI, anterior MI ($p<0.05$), and no thrombolysis ($p=0.05$). Noncardiac death was associated with type-D personality, lack of perceived social support ($p<0.01$), and poor exercise tolerance ($p<0.05$).

TABLE 3 To determine whether type-D was an independent predictor of 6-10 year mortality, we first entered biomedical and psychosocial factors (but not personality type) in a stepwise logistic regression model. This initial analysis yielded a parsimonious group of independent predictors that included impaired left ventricular function, three-vessel disease, poor exercise tolerance, no thrombolysis after MI, hyperlipidemia, and depressive symptoms. Next, we added type-D to this logistic regression model. The final model included type-D but not depression (Table 3). Accordingly, a) type-D was a significant prognostic factor independent of biomedical prognostic factors and b) depression, social alienation, and use of benzodiazepines did not add significantly to the predictive power provided by type-D. Post-hoc analyses indicated that type-D patients, in fact, were more likely to report depression and social alienation ($p<0.00001$), and were more likely to use benzodiazepines ($p=0.0004$).

In addition, multiple logistic regression analyses yielded three independent risk factors for cardiac mortality; i.e., poor exercise tolerance (odds ratio 4.3; 95% CI, 1.6 to 11.6; $p=0.004$), type-D personality (odds ratio 3.8; 95% CI, 1.4 to 10.0; $p=0.0067$) and history of MI (odds ratio 4.7; 95% CI, 1.3 to 17.8; $p=0.021$) and two independent risk factors for noncardiac mortality; i.e., type-D personality (odds ratio 6.4; 95% CI, 1.7 to 23.4; $p=0.0054$) and three-vessel disease (odds ratio 3.6; 95% CI, 1.0 to 12.9; $p=0.046$).

FIGURE 2 Previous reports have shown that CHD patients with a good exercise tolerance have a low mortality risk [32,33]. Consistent with these reports, this subgroup of patients had a low mortality risk in the present study; i.e. 4 out of 32 (13%) for type-D and 5 out of 128 (4%) for no type-D ($p=0.08$). However, patients with a poor exercise tolerance but no type-D did not differ

significantly in mortality from patients with a good exercise tolerance (Figure 2). By contrast, patients with both a poor exercise tolerance and type-D had more than four times the risk for death compared with patients with either a good exercise tolerance or no type-D.

Discussion

The findings of this study indicated that type-D was associated with long-term mortality in men and women with established CHD, after adjustment for the severity of cardiac disease. Consistent with previous reports, biomedical factors such as impaired left ventricular function, three-vessel disease, poor exercise tolerance, history of previous MIs, no thrombolytic therapy, and poor compliance with exercise regimen [1-3] as well as psychosocial factors such as social alienation [6-9], depressive symptomatology [10,11] and use of benzodiazepines [27] were also associated with mortality in the present study. Multivariate analysis indicated that type-D was a significant predictor of mortality independent of biomedical prognostic factors. In addition, this analysis indicated that neither social alienation nor depression added significantly to the predictive power provided by type-D.

These findings are significant for two reasons. First, we found evidence that both biomedical factors and personality are independent predictors of mortality in CHD patients. We focused on the interplay of two broad, stable personality traits; i.e. the tendency to experience negative emotions and the tendency to inhibit self-expression. The presence of only one of these tendencies had no effect; it was the interaction of both tendencies that had an adverse effect on prognosis. Hence, our findings not only relate to those involving emotional distress but also to those involving the chronic suppression of emotions [20-23].

Second, while others have shown that psychosocial stress is an independent predictor in the first years post-MI [6-11], we found evidence that the adverse effect of psychosocial stress on prognosis may extend over a much longer period. The association between type-D and mortality

still was evident 5 years after the coronary event. Hence, it may be valuable to further examine the impact of personality in long-term follow-up studies of CHD patients. The strength of the association between type-D and mortality in this study, as indicated by an adjusted odds ratio of 4.1, warrants additional exploration in confirmatory research.

However, caution should be used in making inferences about the implications of this study. Cardiac rehabilitation may improve survival [2] and emotional well-being [34]; whether type-D would predict mortality in a less selected population of CHD patients is unclear. Accordingly, the findings of this study need replicating in another cohort of CHD patients. Furthermore, the present data are not suited for explicating a causal model. In other words, our findings do not entail that personality was a direct factor in causing mortality [35]. The present study was designed to examine the prognostic power of type-D but not to uncover mechanisms that may account for any associations between personality and mortality. We can therefore only speculate about possible mechanisms that might explain this association.

Personality might promote disease directly through pathophysiological mechanisms. Coronary spasm and activated blood platelets have been shown to play an important role in the progression of CHD and arterial thrombosis [36,37]. Evidence suggests that both coronary spasm [38] and platelet release [37] may be potentiated by exposure to mental stress. Accordingly, silent myocardial ischemia may develop during mental stress testing at relatively low heart rates in patients with CHD [39] and patients with ischemia during mental stress testing are likely to have increased ischemia during sedentary activities in daily life [40]. Silent ischemia due to coronary spasm, in turn, can initiate potentially fatal arrhythmias [41]. Evidence also suggests that depressed patients with CHD have reduced heart rate variability [42] and that reduced heart rate variability may predispose to ventricular fibrillation [43]. It should be noted that personality was related to both cardiac and noncardiac mortality, suggesting that psychosocial stress is

associated with various pathophysiological states [44].

Personality might also promote disease indirectly through health-related behaviors [45]. Failure to change risk factors [46] or poor treatment adherence [47], for example, are related to a greater extent of coronary disease and an increased risk of death in patients with CHD. Their tendency to inhibit behavior in social interaction also entails that type-D patients tend to decrease the availability of social support. Lack of social support is likely to potentiate the role of psychosocial stress in the progression of CHD [48]. In addition, social inhibition may impair communication with physicians which, in turn, may hinder effective treatment [49].

A third possible mechanism implies that personality itself is harmless; i.e., there might be a third variable which is a primary cause of both personality and premature mortality [50]. This proposition entails that type-D merely is a behavioral manifestation of an underlying biological or genetic variable that predisposes an individual to adverse health outcomes. Accordingly, CHD incidence [51] and longevity [52] have been associated with underlying genetic causes. Evidence also suggests that about 50% of individual differences in personality traits such as negative affectivity and social inhibition is due to genetic factors [53,54].

As a consequence, we do not know what therapeutic interventions, if any, would help to decrease mortality in type-D patients with CHD. It certainly is premature to conclude that psychotherapeutic interventions or psychotropic agents would be indicated for these patients. Inclusion of type-D as an individual difference variable in therapeutic trials may provide an answer to the question whether type-D patients may benefit from specific interventions. It should be clear, however, that a link between personality and mortality might mean everything but the fact that the patient is at fault for not being able to control disease [35].

Although the present study precludes definitive conclusions, our findings do support the

notion that stable personality factors may be related to mortality in patients with CHD [4]. Others have shown that adverse health outcomes in CHD are related to social isolation [6-9] and depression [10,11] as well as anxiety [55] and emotional exhaustion [56], and that personality may predict longevity across the lifespan [57]. We found evidence that CHD patients with type-D had a four-fold risk of death compared to patients without type-D.

In conclusion, we showed that the personality effect in this study was a) quite powerful, b) still evident more than 5 years after the coronary event, c) independent of biomedical risk factors, d) evident in men and women, and e) related to cardiac as well as noncardiac death.

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Table 1 **Type-D (or Distressed Type) as Defined by High Scores on Negative Affectivity and Social Inhibition**

		TYPE-D PERSONALITY	PERSONALITY TRAIT	
		Negative Affectivity	Social Inhibition	
		tendency to experience negative emotions	tendency to inhibit self-expression	
Definition	Cluster Analysis * [19]	mean T-score > 60	mean T-score > 55	
	Theoretical Model [17]	high score, defined by median split of scores on corresponding trait measure	high score, defined by median split of scores on corresponding trait measure	
Assessment	Self-Report Scales	"trait-anxiety" scale of the STAI [24]	"social inhibition" scale of the HPPQ [25]	
Correlates to	Clinical	Intrapsychic; tends to be worrying and take gloomy view of things, often feels unhappy or irritated	Interpersonal; tends to keep others at distance, often inhibits expression of true feelings	
	Psychometric [17,19]	Symptoms of depression and chronic tension, low subjective well-being	Low levels of perceived social support	

STAI denotes State-Trait Anxiety Inventory; HPPQ, Heart Patients Psychological Questionnaire.
* Cluster analysis is a statistical procedure that is designed to classify entities into homogeneous subtypes on empirical grounds; T-score= standardized score (mean= 50, SD= 10).

Table 2 **Baseline Biomedical and Psychosocial Characteristics According to Vital Status**

Baseline Characteristics	Vital status at 6-10 years: Survivors (N=265)	Nonsurvivors (N=38)	Univariate p value
Demographic			
Age > 55 years	54 % (144)	66 % (25)	0.18
Gender (male)	89 % (236)	84 % (32)	0.26
Socio-economic (white collar)	59 % (157)	58 % (22)	0.87
Disease Severity			
Impaired left ventricular function *	14 % (36)	34 % (13)	0.001
Three-vessel disease	38 % (100)	63 % (24)	0.003
Noninvasive and Clinical			
Poor exercise tolerance †	43 % (114)	76 % (29)	0.0001
History of MI	71 % (188)	76 % (29)	0.49
One or more previous MIs	11 % (30)	24 % (9)	0.03
Anterior location of MI	29 % (77)	40 % (15)	0.19
Thrombolysis after MI	16 % (30)	3 % (1)	0.05
Aspirin therapy	63 % (167)	53 % (20)	0.22
â-blocker therapy	49 % (129)	55 % (21)	0.45
Angiography after rehabilitation	14 % (36)	13 % (5)	0.94
CABG/PTCA after rehabilitation	9 % (24)	13 % (5)	0.29
Compliance with exercise regimen	92 % (243)	82 % (31)	0.05
Failure to quit smoking	23 % (61)	21 % (8)	0.79
History of hyperlipidemia	30 % (80)	21 % (8)	0.25
Psychosocial			
Type-D personality	23 % (62)	61 % (23)	0.00001
Social Alienation	42 % (112)	66 % (25)	0.006
Depression	39 % (103)	63 % (24)	0.005
Use of Benzodiazepines	19 % (51)	34 % (13)	0.03

Number of subjects appears in parentheses. MI denotes myocardial infarction; CABG, coronary

artery bypass surgery; PTCA, percutaneous transluminal coronary angioplasty.

* left ventricular ejection fraction ≤ 40%; † ≤140 and ≤120 Watt for younger and older men; ≤100 and ≤80 Watt for younger and older women

Table 3 **Predictors of 6-10 Year Mortality, as Determined by Multiple Logistic Regression**

Variable	Odds ratio	95% CI	p value
Type-D personality	4.1	1.9 to 8.8	0.0004
Impaired left ventricular function *	3.0	1.1 to 8.0	0.03
Three-vessel disease	2.4	1.1 to 5.2	0.03
Poor exercise tolerance †	2.4	1.1 to 5.3	0.03
Thrombolysis after MI	0.2	0.3 to 1.2	0.07

CI denotes confidence interval; MI, myocardial infarction.
* left ventricular ejection fraction ≤ 40%; † ≤140 and ≤120 Watt for younger and older men; ≤100 and ≤80 Watt for younger and older women

Figure legends

Figure 1

Percentage of patients who died, stratified by type-D personality after adjustment for severity of disease.

Adjustments were made for left ventricular function (top) and extent of coronary obstructive disease (bottom). Rate of death was 14 deaths out of 64 patients (LVEF≥41% / type-D), 11 deaths out of 190 patients (LVEF≥41% / no type-D), 9 deaths out of 21 patients (LVEF≤40% / type-D), 4 deaths out of 28 patients (LVEF≤40% / no type-D); and 8 deaths out of 48 patients (1-2 vessels / type-D), 6 deaths out of 131 patients (1-2 vessels / no type-D), 15 deaths out of 37 patients (3 vessels / type-D), 9 deaths out of 87 patients (3 vessels / no type-D), respectively. LVEF denotes left ventricular ejection fraction.

Figure 2

Percentage of patients who died, stratified by exercise tolerance and type-D personality.

Number of deaths are presented on top of each bar. Patients with a poor exercise tolerance were stratified by type-D personality. Patients with a good exercise tolerance were pooled (type-D and no type-D).

Dr. Robin Fox, MB, FRCPE
Editor *The Lancet*
42 Bedford Square
London WC1B 3SL
United Kingdom

August 1, 1995

Dear Editor,

Please find enclosed three copies of a manuscript entitled: "Personality as independent predictor of long-term mortality in patients with coronary heart disease." We would appreciate if you would be willing to consider this manuscript for publication in your Journal.

Coronary heart disease still poses a major health problem in terms of excess mortality. Recent research suggests that psychosocial factors, such as depression and lack of social support, are risk factors for mortality in coronary patients. The findings of our study strongly suggest that stable personality traits may account for this detrimental effect of psychosocial stress in coronary patients. We found evidence that type-D personality (i.e. the tendency to suppress emotional distress) was a predictor of 6-10 year mortality in 303 coronary patients, independent of biomedical risk factors. The personality effect in this study was powerful (odds ratio 4.1), still evident more than 5 years after the coronary event, independent of left ventricular function and extent of coronary disease, evident in both men and women, and related to both cardiac and noncardiac death.

The personality model under test in this study is based on sound theoretical and empirical grounds (Denollet et al., *Psychosomatic Medicine* 1995, in press; ref. 16). Please find enclosed three copies of the "in press" reference.

This manuscript is not being submitted elsewhere and has been seen and approved by all authors. We hope that you would be willing to consider this manuscript for publication in *The Lancet*. We are convinced that our findings will interest your readership.

Sincerely yours,

Johan Denollet, Ph.D. Stanislas U. Sys, M.D. Nathalie Stroobant, B.A.

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24 October 1995

Ref.: VC/JG 95/8132 "Personality as Independent Predictor of Long-Term Mortality in Patients With Coronary Heart Disease"

Dear Dr. Choo,

Thank you for your letter of 6 October enclosing your reviewers' comments on the above referenced manuscript. We are convinced that the manuscript is now markedly improved by the revision you recommended. We agree with your reviewers and have revised the manuscript in order to address their commentary.

The personality model under test in this study is now explained in more detail. More specifically, the section on type-D personality was rewritten in order to explain how the definition of this personality type was derived on the basis of multivariate statistical procedures (*Psychol Med* 1992, ref. 19) and theoretical deduction (*Psychosom Med* 1995, ref. 17). Accordingly, the definition of type-D was derived before the mortality outcome was known in the present study. This is now clearly stated in the text. Furthermore, after deleting the 93 subjects of the pilot study (ref. 17) in the statistical analysis, patients with type-D still had four times the risk for death compared with patients without type-D. The results of this analysis are now reported in the results section. Hence, it should be clear that the association between type-D and mortality in the present study was not based on any circular reasoning. Additional analyses also focus on interventional procedures (angiography, CABG, PTCA) that were performed in the follow-up interval. Finally, we analyzed the role of socio-economic status, aspirin therapy, and compliance with exercise regimen as confounding factors. The findings of these additional analyses are reported in the results section (Table 2). Our responses to these comments are detailed in the attached sheets and are highlighted in one copy.

We are convinced that this revision may provide an appropriate answer to your reviewers' comments and we hope that the revised manuscript meets the high standards of *The Lancet*. Please find enclosed five copies of the revised manuscript.

Yours sincerely,

Johan Denollet, Ph.D. Stanislas U. Sys, M.D. Nathalie Stroobant, B.A.

Hans Rombouts, M.D. Thierry C. Gillebert, M.D. Dirk L. Brutsaert, M.D.

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Responses to Comments of Reviewer A.

Thank you for your suggestion to provide more information about what actually happened to the patients in the follow-up interval. It is now pointed out that the medical attention was similar for all patients. Accordingly, it is stated in the Method Section that: "*Standard medical care in the follow-up interval was similar for all patients, and basically consisted of a routine cardiologic check-up every six months*" (page 4, second paragraph, lines 8-9). In response to your suggestion, we conducted additional analyses to examine the role of (a) angiographic investigation and (b) interventional procedures -i.e., CABG/PTCA- in the follow-up interval. In the Method Section, mention is now made of the fact that: "*The frequency of angiography and CABG/PTCA in the follow-up interval was also recorded in this study*" (page 6, second paragraph, lines 8-9).

Results of univariate analyses relating these factors to mortality are reported in Table 2 (page 21): angiography after rehabilitation, 14 % versus 13 %, p=0.94; CABG/PTCA after rehabilitation, 9 % versus 13 %, p=0.29. Hence, angiography and CABG/PTCA in the follow-up interval were not significantly associated with mortality outcomes in the present study.

As you suggested, we also examined the association between type-D personality and the frequency of angiography and CABG/PTCA in the follow-up interval. Univariate analysis indicated that the frequency of angiography after rehabilitation was 17 % versus 12 % for type-D and non-type-D patients, respectively (p=0.35). The frequency of CABG/PTCA after rehabilitation was 13 % versus 8 % for type-D and non-type-D patients, respectively (p=0.21). Hence, type-D patients tended to have more often interventional procedures in the follow-up interval, but this was far from significant.

_____

Responses to Comments of Reviewer B.

Thank you for your constructive comments on our paper. The following sections explain our revision of the paper with reference to the various issues that you indicated in your comments.

As you pointed out, the previous version of our paper lacked a clear rationale for the definition of type-D personality. We agree that the definition of this personality type is germane to the value of the findings reported in our study. Therefore, we revised the paper in order to explain more in detail the way in which the definition of type-D was derived. Among other things, it is now clearly stated that the definition of type-D was derived long before the mortality outcomes were known in the present study. Furthermore, we conducted some of the additional analyses that you suggested. We are convinced that the manuscript has improved by the revision you recommended.

B.1. ***Definition of 'Exposure'***

Although this was not clearly stated in the initial draft of our paper, there certainly was an a-priori reason for the chosen split at the median point on the measures of negative affectivity and social inhibition. This reason for using a median split on both scales to define type-D personality is based on both *empirical induction* and *theoretical deduction*. Accordingly, it is now stated in the text that: "*The present study was preceded by a number of psychological studies defining distinctly different personality types in patients with CHD [17-19]. Personality types can be delineated either through empirical induction (relying on statistical procedures) or through theoretical deduction (relying on specific assumptions). As previously described, we used a combined inductive-deductive approach to analyze the role of personality in the context of CHD [18]*" (page 4, third paragraph).

The *empirical induction* of type-D was derived from a clusteranalytic study that was published in 1992 (Ref. 19; Denollet & De Potter: "Coping subtypes for men with coronary heart disease: Relationship to well-being, stress and Type-A behaviour", Psychological Medicine,22:667-684). We undertook this study because, in our opinion, the question whether or not there are subtypes of CHD patients who display a similar personality profile has been largely overlooked. That is, the notion underlying our research is that CHD patients are heterogeneous with regard to basic personality traits, but that at a higher-order level of analysis a small number of homogeneous personality subtypes can be identified. We initially conducted cluster analysis in patients with established CHD to provide evidence for this hypothesis.

Negative affectivity and social inhibition were selected for the delineation of personality clusters because both basic personality traits are relevant to behavior in a large number of situations and have potential explanatory power in terms of disease-proneness. Negative affect has been related to various adverse health outcomes (e.g., association between depressive symptoms and mortality in myocardial infarction patients, Ref. 10 & 11), while the inhibition of emotional expression may also adversely affect health (e.g., association between suppressed anger and all-cause mortality, Ref. 23). This cluster analytic research yielded a discrete personality profile, which we termed at that time High-Negative Affect or "High-NA" individuals, that represents the empirical basis for the delineation of type-D personality:

- Responses to Comments of Reviewer B (Continued) -

> "High-NA individuals (*characterized* by *high* levels of *negative affectivity* and *social inhibition* ...) reported high levels of transient distress, disability, chronic tension, and anger, and a low level of well-being." (Ref. 19; Denollet & De Potter 1992, p. 679, italics added)

To explain the empirical ground for the definition of type-D, it is now stated in the text that: "*For this purpose, we initially used cluster analysis; i.e., a multivariate statistical procedure that is specifically designed to classify subjects into homogeneous subtypes. This inductive approach yielded a discrete personality type of CHD patients that was characterized by high scores on both negative affectivity and social inhibition [19]. External measures that were not involved in the clustering indicated that these patients were high in emotional distress and low in subjective well-being. The reliability of this personality type was demonstrated across parallel data sets, and follow-up assessment indicated that these patients still experienced substantial distress at 15 months after the initial assessment [19]*" (page 4, last paragraph).

The *theoretical deduction* of type-D was derived from this empirically generated personality profile. The choice of median cut-off points to classify patients was largely based on the Weinberger model of personality types (Weinberger et al.: "Low-anxious, high-anxious and repressive coping styles: psychometric patterns and behavioral and physiological responses to stress", Journal of Abnormal Psychology 1979;88:369-380). In this model, a median cut-off on measures of trait-anxiety and defensiveness was used to define "defensive high-anxious" individuals; i.e., trait-anxiety > median and defensiveness > median.

In our own research, trait-anxiety was more broadly conceptualized as negative affectivity (Denollet, Psychosomatic Medicine 1991; 53:538-556, Ref. 13), and defensiveness was replaced by social inhibition because negative affectivity and social introversion are the major dimensions in the two-dimensional personality/mood space (Meyer & Shack, Journal of Personality and Social Psychology 1989;57:691-706). Hence, by analogy with (a) our own clusteranalytic research and (b) the Weinberger personality model, we used a median cut-off on measures of negative affectivity and social inhibition to define type-D personality (Denollet et al., Psychosomatic Medicine 1995, november/december issue, in press; Ref. 17). Please find enclosed a copy of this *in press* reference.

Accordingly, it is now stated in the Method section of our present paper that: "*On the basis of this empirically generated model, a subsequent study [17] used a deductive approach to define the distressed personality type or type-D in patients with CHD (Table 1). By analogy with cluster analysis, a median split on measures of negative affectivity and social inhibition was used as a definition of type-D; i.e. patients with type-D tend simultaneously to experience negative emotions (as indicated by a negative affectivity score > median) and inhibit self-expression (as indicated by a social inhibition score > median). As a result, type-D is characterized by the chronic suppression of negative emotions across time and situations. Preliminary findings suggested that type-D, in fact, was associated with depression, social alienation, and 2 to 5 year mortality in middle-aged men who survived a MI [17]*" (page 5, second paragraph).

Hence, the allocation of personality type and the choice of cut-off points was based on a-priori grounds and, thus, was made long before the mortality outcome was known. This is now clearly stated in the text of the revised manuscript: " *... the definition of type-D was derived before the mortality outcome was known in the present study*" (page 5, third paragraph, lines 1-2).

As we indicated in our paper, a sub-set of 93 patients participated in a pilot study (i.e., 12 of 105 subjects of the pilot study were excluded in the present study because they had no left ventricular angiogram). As explained earlier, type-D personality was derived before the mortality outcome was known. Although there is some overlap in subject population, the cohort from the present study is in many ways different from that of the pilot study (Ref. 17). That is, the cohort of the pilot study was restricted to men, aged 45 to 60 years, who had survived a myocardial infarction whereas the cohort of the present study does include female and older CHD patients, as well as CHD patients without myocardial infarction. This is illustrated in the following table:

Pilot study [Ref. 17] and *present study*: Differences in cohort.

Characteristic	Pilot Study (N=93)	Present Study (N=303)	*p*-value
Gender (% Female)	0%	12%	$p=0.0006$
Age (Years)	53.6	55.4	$p=0.03$
No myocardial infarction	0%	40%	$p<0.00001$

Nevertheless, your point regarding overlap in subject population is well taken. Therefore, we conducted an additional analysis to examine whether type-D was predictive of mortality in the cohort of patients who did not participate in the pilot study. The findings of this analysis are now reported in the text: "*After deleting the 93 subjects of the pilot study [17] in the analysis, type-D patients still had four times the risk for death compared with patients with another personality; i.e., 21% mortality (13 deaths out of 61) versus 5% mortality (8 deaths out of 149), p=0.0005*" (page 8, paragraph 4, lines 4-6). Hence, the association between type-D and mortality was cross-validated in the cohort of CHD patients that were not involved in the pilot study. Furthermore, the mean follow-up interval was 3.8 years for the pilot study versus 7.9 years for the present study, $p<0.00001$. In our opinion, these observations indicate that the strength of the present study is not affected by the fact that preliminary findings of previous research were based on a sub-set of the cohort.

B.2. ***Choice of cohort***

Mention is now made in the Method Section of the fact that: "*The presence of patients in the Antwerp rehabilitation program is not a function of severity of cardiac disorder, but largely reflects the attitude of referring physicians towards cardiac rehabilitation*" (page 4,

second paragraph, lines 5-8).

- Responses to Comments of Reviewer B (Continued) -

B.3. ***Confounding factors***

Thank you for your suggestion to consider some additional confounding factors that might potentially be important. In response to your suggestion, we conducted additional analyses to examine the role of (a) socio-economic status, (b) aspirin therapy, and (c) compliance with exercise regimen as confounding factors in the present study. In the paragraph on the assessment of clinical risk factors for mortality in CHD (Method Section), it is now stated that: "*Clinical factors included ... no aspirin therapy ... poor compliance with the exercise regimen ...* " (page 6, second paragraph, lines 2-5).

Results of univariate analyses relating these factors to mortality are reported in Table 2 (page 21): socio-economic status (white collar), 59 % versus 58 %, p=0.87; aspirin therapy, 63 % versus 53 %, p=0.22; compliance with exercise regimen, 92 % versus 82 %, p=0.05. While socio-economic status and aspirin therapy were not significantly associated with mortality outcomes, evidence suggested that compliance with exercise regimen is a factor with which to be reckoned in this context. Accordingly, it is now stated in the Results section that: "*Patients who died ... were marginally less likely to ... adhere to the exercise regimen*" (page 9, third paragraph, line 6), and in the Discussion Section that: "*Consistent with previous reports, factors such as ... poor compliance with exercise regimen ... were also associated with mortality in the present study*" (page 11, first paragraph, lines 3-7). However, adherence to exercise regimen was not retained in the multiple logistic regression model as an independent predictor of mortality.

Responses to Comments of Reviewer C.

Thank you for your many helpful comments that enabled us to strengthen our paper. We hope that the following responses may provide an appropriate answer to the various issues that you have indicated.

Your point regarding the definition of type-D personality is well taken. We agree that the previous version of our paper failed to explain how the definition of type-D personality was reached on the basis of our previous research. For this reason, the section on 'Type-D Personality' (pages 4 and 5) was rewritten and now contains new paragraphs in order to explain how the definition of type-D was derived.

As you correctly pointed out, definition of this personality type on the basis of the mortality data of the present study certainly would diminish the value of our paper. However, the definition of type-D was derived long before the mortality outcomes were known in the present study. We also agree that the relative mortality risk of about 4 that is associated with type-D is striking. Nevertheless, this figure is consistent with findings reported by others; e.g., Frasure-Smith et al. found a relative mortality risk of more than 6 for myocardial infarction patients who complained about depressive symptoms (Circulation 1995;91:999-1005; Ref. 11).

C.1. ***Definition of type-D personality***

The delineation of type-D is not just a fortunate choice, but is based on both *empirical induction* and *theoretical deduction*. Accordingly, it is now stated in the section on type-D personality that: "*The present study was preceded by a number of psychological studies defining distinctly different personality types in patients with CHD [17-19]. Personality types can be delineated either through empirical induction (relying on statistical procedures) or through theoretical deduction (relying on specific assumptions). As previously described, we used a combined inductive-deductive approach to analyze the role of personality in the context of CHD [18]*" (page 4, third paragraph).

The empirical induction of type-D was derived from a clusteranalytic study that was published in 1992 (Ref. 19; Denollet & De Potter: "Coping subtypes for men with coronary heart disease: Relationship to well-being, stress and Type-A behaviour", Psychological Medicine,22:667-684). We undertook this study because in our opinion, biobehavioral researchers have treated patients with coronary heart disease (CHD) as homogeneous entities in terms of basic personality traits. A great deal of effort has been devoted to specific components such as hostility and anger-in, whereas the question whether or not there are subtypes of CHD patients who display a similar personality profile has been largely overlooked. With reference to this issue, the notion underlying our research is that CHD patients are heterogeneous with regard to basic personality traits, but that at a higher-order level of analysis a small number of homogeneous personality subtypes can be identified. We initially conducted cluster analysis in patients with established CHD to provide evidence for this hypothesis.

We selected negative affectivity and social inhibition for the delineation of personality clusters because both basic personality traits are relevant to behavior in a large number of situations and have potential explanatory power in terms of disease-proneness. Negative

affect has been related to various adverse health outcomes (e.g., association

between depressive symptoms and mortality in myocardial infarction patients, Ref. 10 & 11), while the inhibition of emotional expression may also adversely affect health (e.g., association between suppressed anger and all-cause mortality, Ref. 23). This cluster analytic research yielded a discrete personality profile, which we termed at that time High-Negative Affect or "High-NA" individuals, that represents the empirical basis for the delineation of type-D personality:

> "High-NA individuals (*characterized* by *high* levels of *negative affectivity* and *social inhibition* ...) reported high levels of transient distress, disability, chronic tension, and anger, and a low level of well-being." (Ref. 19; Denollet & De Potter 1992, p. 679, italics added)

Accordingly, it is now stated in our present paper that: "*For this purpose, we initially used cluster analysis; i.e., a multivariate statistical procedure that is specifically designed to classify subjects into homogeneous subtypes. This inductive approach yielded a discrete personality type of CHD patients that was characterized by high scores on both negative affectivity and social inhibition [19]. External measures that were not involved in the clustering indicated that these patients were high in emotional distress and low in subjective well-being. The reliability of this personality type was demonstrated across parallel data sets, and follow-up assessment indicated that these patients still experienced substantial distress at 15 months after the initial assessment [19]*" (page 4, last paragraph).

On the basis of this empirically generated personality profile, we used a deductive strategy for the definition of type-D personality in patients with CHD. This definition was largely based on the Weinberger model of personality types (Weinberger et al.: "Low-anxious, high-anxious and repressive coping styles: psychometric patterns and behavioral and physiological responses to stress", Journal of Abnormal Psychology 1979;88:369-380). In this model, a median cut-off on measures of trait-anxiety and defensiveness was used to define "defensive high-anxious" individuals; i.e., trait-anxiety > median and defensiveness > median. In our research, trait-anxiety was more broadly conceptualized as negative affectivity (Denollet, Psychosomatic Medicine 1991; 53:538-556, Ref. 13), and defensiveness was replaced by social inhibition because negative affectivity and social introversion are the major dimensions in the two-dimensional personality/mood space (Meyer & Shack, Journal of Personality and Social Psychology 1989;57:691-706). Hence, by analogy with (a) our own clusteranalytic research and (b) the Weinberger personality model, we used a median cut-off on measures of negative affectivity and social inhibition to define type-D personality (Denollet et al., Psychosomatic Medicine 1995, november/december issue, in press; Ref. 17). Please find enclosed a copy of this *in press* reference.

Accordingly, it is now stated in the Method section of our present paper that: "*On the basis of this empirically generated model, a subsequent study [17] used a deductive approach to define the distressed personality type or type-D in patients with CHD (Table 1). By analogy with cluster analysis, a median split on measures of negative affectivity and social inhibition was used as a definition of type-D; i.e. patients with type-D tend*

simultaneously to experience negative emotions (as indicated by a negative affectivity score > median) and inhibit self-expression (as indicated by a social

- Responses to Comments of Reviewer C (Continued) -

inhibition score > median). As a result, type-D is characterized by the chronic suppression of negative emotions across time and situations. Preliminary findings suggested that type-D, in fact, was associated with depression, social alienation, and 2 to 5 year mortality in middle-aged men who survived a MI [17]" (page 5, second paragraph).

As a consequence, the association between type-D and mortality in the present study was not based on any circular reasoning. Hence, it is now stated in the text that: " ... *the definition of type-D was derived before the mortality outcome was known in the present study*" (page 5, third paragraph, lines 1-2).

The subject population of the pilot study (Ref. 17) was restricted to men, aged 45 to 60 years, who had survived a myocardial infarction, and the follow-up interval in that study was only 2 to 5 years. The subject population of the present study also includes female and older CHD patients, as well as CHD patients without myocardial infarction. We also conducted additional analyses to examine whether type-D was predictive of mortality in the cohort of patients who did not participate in the pilot study reported in reference 17. The findings of this analysis are now reported in the Results section: "*After deleting the 93 subjects of the pilot study [17] in the analysis, type-D patients still had four times the risk for death compared with patients with another personality; i.e., 21% mortality (13 deaths out of 61) versus 5% mortality (8 deaths out of 149), p=0.0005*" (page 8, paragraph 4, lines 4-6). Hence, type-D was related to mortality in CHD patients that were not involved in the definition of this personality type.

C.2. ***Other psychological variables in the present study***

In the present study, type-D was validated against two psychological variables that have been shown by others to be independent predictors of mortality in patients with CHD; i.e., *social alienation* and *depression*. Mention is made in the Introduction Section of the fact that: " ... *particular factors such as social alienation [6-9] and depression [10,11] have been associated with a poor prognosis in patients who survived a myocardial infarction*" (page 3, first paragraph, lines 4-6). To our knowledge, these are the only psychological variables that have been consistently related to mortality in CHD. Accordingly, it is stated in the Method section that: "*Social alienation and depression were measured by the Millon Behavioral Health Inventory (MBHI) [26] in the present study to examine the hypothesis that type-D may explain the association between these particular psychosocial factors and mortality in CHD patients [6-11]*" (page 6, last paragraph, lines 1-3). As discussed in the text, the 'social alienation' scale of the MBHI measures perception of lack of social support, while the 'pessimism' and 'despair' scales of the MBHI measure cognitive dimensions of depression. We also used an external measure of distress in this study: "*In addition, use of benzodiazepines was conceptualized as a non-test marker of emotional distress. Use of benzodiazepines has been related to a poor prognosis in MI patients [17,27]*" (page 7, lines 1-2).

Results of univariate analyses relating these psychological variables to mortality are reported in Table 2 (page 21): social alienation, 42% versus 66%, p=0.006; depression,

39% versus 63%, p=0.005; benzodiazepines, 19% versus 34%, p=0.03. It is stated in the Results section of the text that: "*Patients who died ... were more*

likely to have ... complaints of social alienation, depressive symptoms, benzodiazepine-abuse, ... " (page 9, third paragraph, lines 1-5). However, none of these variables was retained in the multiple logistic regression model including type-D and biomedical risk factors: " *... depression, social alienation, and use of benzodiazepines did not add significantly to the predictive power provided by type-D. Post-hoc analyses indicated that type-D patients, in fact, were more likely to report depression and social alienation (p<0.00001), and were more likely to use benzodiazepines (p=0.0004)*" (page 10, first paragraph, lines 8-11).

Accordingly, mention is made in the Discussion to the fact that: "*Consistent with previous reports, ... psychosocial factors such as social alienation [6-9], depressive symptomatology [10,11] and use of benzodiazepines [27] were also associated with mortality in the present study. Multivariate analysis ... indicated that neither social alienation nor depression added significantly to the predictive power provided by type-D*" (page 11, first paragraph, lines 6-10). In our opinion, these findings suggest the validity the type-D against other psychological variables with potential predictive power.

C.3. ***Other cut-offs***

As discussed above, we used a median split on measures of negative affectivity and social inhibition by analogy with the Weinberger personality model. In response to your suggestion, we conducted some additional analyses using different cut-offs. When type-D was defined by a cut-off at the 60th centile for both negative affectivity and social inhibition, 61 of 303 subjects (20%) were classified as type-D. In this case, the association between type-D and mortality remained significant; i.e., 26% mortality vs. 9% mortality for type-D patients and non-type-D patients, respectively (p=0.0003). Likewise, type-D as defined by a cut-off at the 40th centile still was associated with mortality (p=0.009).

Furthermore, the Results section contains an alternative classification system to examine the role of negative affectivity and the role of social inhibition *per se*. In this alternative classification, type-D is compared with *high anxiety/low inhibition* and *high inhibition/low anxiety* categories, respectively. This analysis clearly indicated that it was the interaction of high negative affectivity with high social inhibition that was associated with an increased mortality risk: "*Rate of death for patients scoring high on trait-anxiety but low on social inhibition (4 of 66= 6%) was smaller than that for type-D patients (p=0.0008) and did not differ from that for patients scoring low on trait-anxiety (11 of 152= 7%), p=0.75. Likewise, rate of death for patients scoring high on social inhibition but low on trait-anxiety (5 of 81= 6%) was smaller than that for type-D patients (p=0.0003) and did not differ from that for patients scoring low on social inhibition (10 of 137= 7%), p=0.75. Accordingly, it was not trait-anxiety or social inhibition per se but rather the interaction of trait-anxiety with social inhibition that was predictive of mortality*" (page 9, second paragraph, lines 4-11).

Hence, we believe that the findings of these additional analyses, together with the empirical-theoretical basis for the definition of type-D, clearly indicate that the present

definition of type-D was not just a fortunate choice.

- Responses to Comments of Reviewer C (Continued) -

C.4. ***Conclusions***

In the Discussion section, greater emphasis is now placed on the fact that: " ... *the findings of this study need replicating in another cohort of CHD patients*" (page 12, first paragraph, line 4).

Minor points

C.5. Thank you for pointing out this error in the text. "Controlling for time of death" is now deleted and replaced by the statement that: " ... *we conducted univariate analyses after stratifying patients by time of death ...* " (page 7, last paragraph, lines 2-3).

C.6. Because the length of survival time was not an outcome measure in the present study, we decided to use multiple logistic regression analysis to identify independent predictors of mortality. This decision was made by analogy with the statistical analysis of data reported by Berkman et al. (Ref. 7, "Emotional support and survival after myocardial infarction", Annals of Internal Medicine 1992;117:1003-1009) and Frasure-Smith et al. (Ref. 11, "Depression and 18-month prognosis after myocardial infarction", Circulation 1995;91:999-1005). Accordingly, our findings of multivariate analyses can be compared with the findings of these authors.

C.7. The statement that "The association between type-D and mortality was not related to cause of death ... " is now deleted and replaced by the statement that: "*Type-D ... was associated with cardiac death (15 of 77=20% versus 9 of 212=4%, p=0.00003) as well as noncardiac death (8 of 70=11% versus 6 of 209=3%, p=0.009)*" (page 9, second paragraph, lines 1-4).
