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Impact of Cardiac Rehabilitation and Exercise Training on Psychological Risk Factors and Subsequent Prognosis in Patients with Cardiovascular Disease

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**Abbreviations**

ANS = Autonomic nervous system  
CHD = Coronary heart disease  
CR = Cardiac rehabilitation  
CRET = Cardiac rehabilitation and exercise training  
CRF = Cardiorespiratory fitness  
CVD = Cardiovascular disease  
ET = Exercise training  
HF = Heart failure  
PA = Physical activity  
PS = Psychosocial stress  
SMT = Stress management training  
$\text{VO}_2$ = Oxygen consumption
Abstract

The role of psychological risk factors has been under-recognized in most subspecialties of medicine, as well as in general medicine practices. However, considerable evidence indicates that psychosocial factors are involved in the pathogenesis and progression of cardiovascular disease (CVD). Emerging data from cardiac rehabilitation (CR) settings and CR-based exercise training (CRET) programs have demonstrated the value of comprehensive CR and exercise training to improve psychological functioning and reduce all-cause mortality. Recent evidence also supports the role of CRET and the added value of stress management training in the secondary prevention of CVD.

Summary for Online Listing

Psychological risk factors are involved in the pathogenesis of cardiovascular diseases (CVD) and impact prognosis in patients with CVD. Cardiac Rehabilitation and Exercise Training (CRET) programs lead to significant improvements in CVD risk factors, particularly improving levels of cardiorespiratory fitness, and psychological risk factors and stress-related increased mortality risk. Efforts are needed to increase awareness of the impact of psychological stress in CVD and to increase referral and delivery of CRET.
There is considerable evidence that psychosocial stress (PS) plays an important role in the pathogenesis and progression of cardiovascular disease (CVD).\textsuperscript{1-3} Despite the widespread belief by lay people that PS worsens many medical conditions, including CVD, we believe that the importance of stress has been unrecognized or underappreciated by the medical community, especially among practitioners in CVD.\textsuperscript{1-4} PS is one of the most frequent complaints from patients, and PS adversely impacts numerous important medical conditions, including most chronic diseases (cancer, diabetes mellitus, arthritis, lung disease, human immunodeficiency virus), as well as CVD.\textsuperscript{1-6} Certainly, the link between PS and CVD is becoming increasingly better established.\textsuperscript{1-6}

Cardiac rehabilitation and exercise training (ET; CRET) programs are an integral part of providing optimal medical therapy to patients with established coronary heart disease (CHD).\textsuperscript{7-9} Substantial data from CRET programs have demonstrated dramatic improvements in exercise capacity or cardiopulmonary fitness (CRF), various CHD risk factors (lipids, glucose, blood pressure, inflammation), as well as measures of PS and quality of life.\textsuperscript{7,8} Although no single study has demonstrated major reductions in morbidity and mortality, with few exceptions, most major meta-analyses over the past 3 decades have demonstrated reductions in morbidity and mortality.\textsuperscript{9,10}

In this select review of the area, we discuss the role of PS to impact CVD, the high prevalence of PS in patients with CVD, especially CHD, and the impact of CRET to reduce PS and PS-associated mortality risk. Finally, we review recent evidence on the potential importance of
stress management training (SMT) to further reduce PS and major clinical end-points when added to routine CRET programs.

**Does Psychological Stress Increase Cardiovascular Disease Risk?**

We believe that the topic of PS has been under-recognized by clinicians in most medical specialties, especially specialties in CVD.\(^1\)\(^-\)\(^6\) However, the lay public has been extremely interested in this topic in general and on the impact of PS on CVD.\(^4\) Over the past 2 decades, the link between PS and CVD has become increasingly well-established.\(^1\)\(^-\)\(^6\)

Epidemiological data and prospective studies have explored the complex relationship between PS and CVD.\(^1\)\(^-\)\(^6\) When PS has been assessed by validated screening instruments, the clinical impact of PS has been comparable with many of the major CHD risk factors, including smoking, hypertension and low physical activity (PA).\(^1\)\(^-\)\(^6\) Although most of the literature in PS has focused on depression and CVD, there is substantial evidence that other components of PS, including anxiety, hostility, isolation, strong adverse emotions, time urgency, and total PS, have significant impact on acute and chronic aspects of CVD.\(^1\) Certainly there is substantial evidence that PS plays an important role in the pathogenesis of CVD and on recovery following major CVD events (Figure 1).\(^5\) Indeed, PS disturbs cardiometabolic function, which may result in insulin resistance, HTN, inflammation, hyperglycemia and other metabolic disorders that may worsen endothelial dysfunction, which is a common denominator in CVD. Also, practical issues may be involved, such as patients with greater PS engage in maladaptive, health-damaging behaviors, such as nonadherence with various aspects of the medical regimen, including
nonpharmacologic and drug treatment regimens, poor health habits, as well as substance abuse.\textsuperscript{5,11}

Arguably the most important epidemiologic data on the critical role of PS and CHD comes from the INTERHEART study,\textsuperscript{12} which evaluated major CHD risk factors and PS among a diverse group of 11,119 myocardial infarction patients and 13,648 age-and gender-matched control subjects from 52 countries and 262 centers. This landmark study demonstrated that among 9 major modifiable CHD risk factors, PS was third behind only lipids and smoking in importance, and PS accounted for close to 1/3 the total attributable risk for acute infarction. In addition, epidemiological and laboratory studies have demonstrated that mental stress may provoke myocardial ischemia in the laboratory and during daily life, and mental stress-induced myocardial ischemia is associated with worse prognosis, over and above exercise testing.\textsuperscript{5,13,14}

Potential reasons for these findings are numerous, but particularly important is that the autonomic nervous system (ANS) probably plays a significant role in mediating the effects of PS and CVD.\textsuperscript{11,15,16} Chronic imbalance of the ANS, with a shift toward higher sympathetic as opposed to parasympathetic/vagal tone, may worsen CVD prognosis. In fact, over activation of the sympathetic nervous system may worsen endothelial function and coronary artery tone and predispose to various rhythm disorders, platelet activation and thrombosis, as well as elevated blood pressure and left ventricular hypertrophy, whereas parasympathetic activation or withdrawal has beneficial and adverse effects on CVD, respectively. Many forms of PS will alter the balance between sympathetic to vagal tone, which clinically may be manifest as reduced heart rate variability, increased resting heart rate, blunted exercise heart rate and delayed heart
rate recovery following exercise, all evidence of ANS dysfunction that may increase the risk of CVD events.

**PS and CVD**

Although there are many aspects of PS which may worsen CVD, our research has largely focused on anxiety, hostility (or un-expressed anger) and depression in CHD.

Anxiety and CVD. Although probably less established than is the relationship of depression with CVD, a causal relationship has been suggested between anxiety and CVD.\(^1\,^{17,18}\) Several studies have suggested that anxiety may be an independent predictor of CHD morbidity and mortality.\(^1\,^{5,19,20}\) Elevated anxiety symptoms have been shown to be associated with a 2-fold increased risk of mortality in patients who have had coronary artery bypass graft surgery\(^21,22\) and in outpatients with CHD.\(^23,24\) Frasure-Smith and colleagues\(^25\) reported that CHD patients with generalized anxiety disorder assessed two months following hospital discharge showed a 2.3-fold increased risk of adverse CVD events, and Strik et al.\(^26\) reported a 2.8-fold increased risk of adverse events in acute post-infarct patients in which anxiety was measured one month following hospital discharge. Similarly, a 2-fold increased risk of adverse events was observed in stable CHD patients\(^21\) and in patients with elevated anxiety during annual clinic visits.\(^27\) Elevated anxiety symptoms in the coronary care unit are associated with increased mortality within the first years post-acute infarction.\(^28\) Anxiety appears to be prevalent among patients with CVD, perhaps more so in the younger CHD patients (Figure 2).\(^18\)
Type A Behavior, Hostility and CVD. Friedman and Rosenman\textsuperscript{29} first defined persons who exhibited an emotional syndrome characterized by a continuously harrying sense of time urgency, aggressiveness, ambitiousness, competitive drive, and easily aroused-free floating hostility as having type A behavior pattern. Hostility, or cynical attitudes and distrust, as well and feeling of anger, have been linked to dyslipidemia, hypertension, inflammation, obesity, and atherosclerosis.\textsuperscript{1,30-34} Epidemiologic studies indicate that hostility has been linked to up to 5-fold increased risk of major CHD events.\textsuperscript{1,35-37} As with anxiety, younger patients have a much higher prevalence of hostility than do older CHD patients (Figure 2).\textsuperscript{18}

Depression and CVD. Probably the strongest evidence for the link between PS and CVD comes from the data on depression in CVD and CHD. In fact, numerous population studies have demonstrated highly statistically significant correlation between depression and increased risk of future CHD events.\textsuperscript{1-6} Prevalence rates of major depressive disorder among patients with CHD have been estimated to be as high as 25\%, with point prevalence rates estimated at up to 45\% for patients with minor depression or elevated depressive symptoms.\textsuperscript{38} Depression also has been associated with more than a 2-fold increased risk for patients undergoing bypass surgery.\textsuperscript{39} In one meta-analysis of 20 prospective studies of patients with CHD, depressive symptoms were associated with an odds ratio of 2.24 for mortality.\textsuperscript{40} The American Heart Association recently recognized depression as a risk factor for patients with CHD, and encouraged routine assessment of depressive symptoms.\textsuperscript{41} Additionally, Grace and colleagues\textsuperscript{42} demonstrate that depression at the time of CVD hospitalization not only impacted quality of life but also subsequent mortality. A sense of hopelessness, particularly, seems to be strongly correlated with adverse CVD outcomes. Major studies have demonstrated a very high prevalence of depression among CHD
patients, probably moreso in women, and slightly moreso in younger as opposed to older CHD patients, although older patients have much higher prevalence of depression than anxiety or hostility (Figure 2). Patients with diabetes seem to particularly have a high prevalence of depression.

**Impact of CRET on PS**

We and others have demonstrated the powerful effects of CRET and improvements in CRF on PS and PS-induced mortality.

Role of CRET in Anxiety. Patients with CHD, especially younger patients, have a very high prevalence of anxiety (Figure 2). Following formal CRET, the prevalence of anxiety (Kellner Anxiety Score > 7) and high anxiety (Kellner Anxiety Score > 10) fell by 56% and 69%, respectively in one study, and then in another study fell by 61% in younger patients and by 32% in older CHD patients (Table 1). A meta-analysis mostly from CVD cohorts also demonstrated that ET significantly reduced anxiety symptoms.

Role of CRET in Hostility. Over fifteen years ago, we demonstrated that following CRET, hostility, which is often defined as unexpressed anger and defined in our study as Kellner Hostility Score > 7, fell from 28% at baseline to 15% in young patients and from 8% to only 4% in those older than 65 years. In a more recent study (Figure 2, Table 1), we demonstrated greater than 50% reductions in the prevalence of hostility in both younger and older CHD patients.
Impact of CRET on Depressive Symptoms. Probably the most powerful evidence of the role of CRET in secondary CHD prevention is in patients with depression. Although depressive symptoms seem to be prevalent in CHD patients regardless of age, the prevalence of depressive symptoms (Kellner Depression Score > 6) seems to be especially high in CHD patients with diabetes and in women. However, following formal CRET programs, the prevalence of depression generally is reduced by over 50%.

Especially noteworthy is the impact of CRET to reduce not only depressive symptoms but depression-related increased mortality. In a study of 522 consecutive CHD patients enrolled in CRET and in 179 CHD patients who did not complete CRET, we assessed the impact of depressive symptoms on subsequent survival. Following CRET, the prevalence of depressive symptoms fell from 17% to only 6% (minus 63%; p<0.001). Moreover, depressive symptoms in CHD patients following CRET had a 4-fold higher mortality than did non-depressed patients, and in those with baseline depressive symptoms who completed CRET, mortality was 73% lower compared with depressed patients who did not participate in formal CRET programs (8% versus 30%; p=0.005). Since CRET involves more than just ET intervention, as discussed in detail in this Symposium, we assessed changes in CRF and subsequent risk of depression and mortality. Using cardiopulmonary gas exchange to precisely assess CRF before and after CRET, we demonstrated that those who did not improve their peak oxygen consumption (peak VO₂) continued to have a high prevalence of depressive symptoms and high mortality risk during follow-up (Figure 3). However, those who either had small improvements or more marked improvements in peak VO₂ both had striking reductions in the prevalence of depressive
symptoms and depression-related increased mortality risk. In a randomized control trial of 101 CHD patients, ET and sertraline therapy both resulted in greater reductions in depressive symptoms and improvements in heart rate variability compared with placebo, although there appeared to be a trend to greater benefit with ET than with sertraline (p=0.09). 49

The HF :ACTION was a large randomized trial of ET versus usual care in 2,322 patients with systolic heart failure (HF) and demonstrated significant benefits of ET over usual care in both reducing depression symptoms and clinical events, despite only inducing a mean improvement in peak VO₂ of 4%. 50 We also assessed the impact of CRET on depression and survival in CHD patients with systolic HF. 51 Similar to non-HF patients with CHD, depression fell from 22% to 13% following CRET (- 40%; p<0.001). Those who were initially depressed and who remained depressed following CRET had a 4-fold higher mortality than did HF patients whose depression resolved with CRET (43% versus 11%; p=0.005). Additionally, HF patients who completed CRET had considerably lower mortality than did HF patients who did not complete CRET (18% versus 44%; - 59%; p<0.005). As with non-HF patients, the survival benefits following CRET are mostly noted in depressed HF patients who significantly improved peak VO₂ following CRET (Figure 4). 51

Benefits of CRET on Total PS. We previously assessed 500 consecutive CHD patients and demonstrated that improvements following CRET were similar or even greater in those with high as opposed to low PS (based on combined Kellner scores for depression, anxiety, hostility, and somatization.) 52 In another study, we combined Kellner scores for anxiety, hostility and depression for a total PS score, which predicted mortality in 522 consecutive CHD patients. 53 In
fact, almost all of the mortality during follow-up was noted in those with high PS who did not improve CRF (defined as <10% improvement in peak VO$_2$ following CRET). On the other hand, patients with low PS at baseline and those with high PS who significantly improved their peak VO$_2$ by at least 10% had low 3-year mortality (Figure 5).$^{53}$

Finally, in a study of 538 who completed CRET, we assessed whether other PS contributed to mortality risk.$^{54}$ Following CRET, we compared mortality in 502 non-depressed patients with mortality in 14 patients with depressive symptoms alone and 22 patients with depressive symptoms combined with anxiety and/or hostility symptoms. Although there was a trend of higher mortality in the comorbid depression group compared with depression alone (23% versus 14%; p=NS), the overall impact was largely driven by depressive symptoms (19% mortality versus 3% in non-depressed patients; p<0.001). This study was limited, however, by the fairly low prevalence of PS following formal CRET.

**Addition of Stress Management Training to Routine CRET**

In a series of studies of patients with mental-stress induced myocardial ischemia, Blumenthal and colleagues reported that patients randomized to either SMT or ET had better clinical outcomes compared to non-randomized usual care controls.$^{55}$ Moreover, SMT and ET produced complementary benefits: SMT reduced mental stress-induced ischemia while ET reduced exercise-induced ischemia. In a subsequent, fully randomized trial, SMT and ET each produced comparable improvements in psychological functioning as well as greater improvements in biomarkers of CVD risk compared to usual care controls.$^{56}$ While these studies compared ET to SMT, more recently, Blumenthal and colleagues$^{57}$ examined the combined benefit of ET and
SMT. In the ENHANCED trial, 151 CHD patients were randomized to standard CRET or comprehensive CRET combined with SMT; a matched group of CRET-eligible patients who did not attend CRET comprised a comparison group. During follow-up of 5.3 years (median 3.2 years), patients randomized to SMT, consisting of combined education, group support and cognitive behavior therapy delivered in 12 weekly 1.5 hour sessions in groups of 4-8 participants, exhibited greater reductions in composite PS levels compared with CRET alone (p=0.022), an effect that was driven primarily by reductions in anxiety, distress and perceived stress. Both CRET groups had lower composite clinical event rates compared with the non-CRET comparison group (hazard ratio/HR 0.44; confidence interval/CI 0.27-0.71; p<0.001) but CRET +SMT had lower clinical events than did CRET alone (18% versus 33%; HR 0.49; CI 0.25 – 0.95; p=0.04), suggesting additional benefit for adding SMT to routine CRET therapy to enhance secondary prevention of CHD (Figure 6).

Interestingly not all studies have found SMT to improve clinical outcomes. In a study of 2,328 post-infarction patients randomized to 7 weekly sessions of SMT or usual care and followed for 12 months, Jones and West\textsuperscript{58} reported that prevalence rates of anxiety and depression remained high and there were no important group differences following treatment and no differences in major clinical end-points. In 1,376 post-MI patients, Frasure-Smith and colleagues\textsuperscript{59} randomized patients to telephone-based SMT versus usual care, and also found no group differences in PS or clinical outcomes during follow-up. The ENRICHD trial\textsuperscript{60} studied 2400 post MI patients with depression or who reported low social support and assessed the impact of cognitive-behavior therapy versus usual care. Although the intervention group demonstrated modest 2 point differences in the Beck Depression Inventory compared with usual care, there were also no
significant impacts noted on major clinical events. In contrast, the most recent study by Blumenthal and colleagues\textsuperscript{57} compared SMT/CRET with CRET alone and demonstrated additional effects of SMT when combined with the already well-proven effects of ET-based formal CRET intervention. These data suggest that the combination of SMT and CRET is especially effective. Further studies are needed to determine whether SMT can be combined with new models of CRET, which are needed to enhance the delivery and effectiveness of CRET programs in the modern era.\textsuperscript{9}

**Potential Mechanisms for PS Benefits**

The mechanism by which behavioral factors and PS contribute to CVD and CHD is not completely understood but likely multifactorial, including worsening CHD risk factors which contribute to atherosclerosis, adverse effects on the ANS, inflammation, enhanced platelet activation, circulating catecholamines, cortisol, reduced myocardial ischemia, and enhanced coronary vasoreactivity and constriction.\textsuperscript{1,18-18,30,48} Likewise, an improvement in risk factors and PS following CRET is also probably multifaceted. Certainly, the CRET programs are centered around increasing PA and ET to improve CRF, which correlates with most of the improvements and prognosis with CRET therapy in general and for PS. However, CRET also has beneficial effects on certain emotions and improving ANS function,\textsuperscript{16} and improves inflammation,\textsuperscript{61,62} metabolic syndrome,\textsuperscript{63,64} and blood rheology.\textsuperscript{65} Some evidence suggests that ET also has favorable effects on brain plasticity and cognition.\textsuperscript{66,67} In fact, CRET involves more than just ET, and other aspects of the Phase II CRET programs involve education of the patients and their significant others, which may also be important by increasing understanding of the underlying
disease process and its manifestations, therefore "empowering" patients to modify their own recovery, which is a process called "information involvement," which may also enhance coping mechanisms as well as emotional and social recovery processes.\textsuperscript{66,67} In addition, CRET programs have aspects of "group therapy," that is often used by psychologists and psychiatrists that may promote socialization and bonding with other patients in CRET who are at various stages in their recovery process.\textsuperscript{66,68} Despite the significant improvements in PS following CRET, many patients continue to experience PS following CRET and have high morbidity and mortality. Further therapy directed at PS, including behavior modification, psychotherapy, and/or pharmacologic intervention could be required.\textsuperscript{66,69,70} The recent data with SMT seems particularly attractive for improving the already substantial improvements noted with CRET.\textsuperscript{57}

\textbf{Limitations}

Several limitations of the studies discussed in this paper should also be noted. Many of the Ochsner studies were not randomized, which raises the possibility of non-specific effects, regression to the mean or selection bias. However, since CRET programs are well established around the world\textsuperscript{7-9,71-73} it is difficult to randomize patients to no CRET therapy in which they would be denied what is now considered the standard of care for patients with CVD. Also, much of the data that we presented comes from a single center (Ochsner Medical Center in New Orleans, LA) with a strong clinical and research emphasis on CRET and PS, so other CRET investigators also need to evaluate the impact of CRET and unique CRET delivery systems on psychological risk factors and subsequent prognosis.
**Conclusion**

Substantial evidence suggests that PS has adverse effects on the pathogenesis and progression of CVD and adversely impacts prognosis following major CHD events. Although most of the evidence has focused on the role of depression in CVD, other aspects of PS, including anxiety, hostility, and total PS, also may impact prognosis in CVD. Following formal CRET programs, substantial evidence indicates that CRET markedly reduces PS and PS-related increased mortality rates. Recent evidence suggests that the benefits of CRET may be further enhanced with the addition of SMT to patients receiving CRET intervention. Other CRET investigators need to also evaluate the impact of CRET and unique CRET delivery systems on psychological risk factors and subsequent prognosis. Finally, considerably greater emphasis is needed on PS and its intervention, especially with CRET, in the secondary prevention of CVD and, especially, CHD.

*It is exercise alone that supports the spirit, and keeps the mind in vigor.* – Cicero⁷⁴
References


68. Kulik JA, Mahler HI. Social support and recovery from surgery. *Health Psychol* 1989;8:221-238.


Figure Legend

1. Several reasons for interest by medical practices in the evaluation and treatment of psychosocial stress. CHD = coronary heart disease. Reproduced with permission from Rozanski A et al.¹⁵

2. Prevalence of adverse behavioral characteristics in young (mean ± SD, 48 ± 6 years) and older (mean ± SD, 75 ± 3 years) patients with CHD. Reproduced with permission from Lavie CJ et al.¹⁸

3. Prevalence of depression and subsequent mortality based on changes in peak VO₂ during cardiac rehabilitation and ET. *P <.001 compared with VO₂ loss. Reproduced with permission from Milani RV et al.⁴⁸

4. Actuarial hazard for death comparing patients with HF with and without depression stratified by change in oxygen uptake after ET (p <0.01 between oxygen uptake loss/depressed and all others). Reproduced with permission from Milian RV et al.⁵¹

5. Actuarial cumulative hazard plot for survival time based on changes in exercise capacity (high exercise change vs low exercise change) after ET split by baseline psychosocial stress (high psychosocial stress vs low psychosocial stress; n = 522). Reproduced with permission from Milani RV et al.⁵³

6. Cumulative time-to-event curves for clinical events in the CR+SMT, CR-alone, and No-CR groups. Clinical events included all-cause mortality, myocardial infarction, cardiac or peripheral vascular intervention, stroke/TIA, or unstable angina requiring hospitalization. Participants in the CR+SMT were at significantly lower risk of clinical events compared with the CR-alone group (HR= 0.47 [0.24, 0.91], P = 0.025). Both CR groups had lower
event rates compared with a non-randomized, matched No-CR control group (HR = 0.35 [0.22, 0.56], P < .001). Number at risk represents participants with follow-up data for clinical events who had not yet had an event at years 0, 2, and 4. Reproduced with permission from Blumenthal JA et al. 57
Table 1. Effects of Cardiac Rehabilitation and ET Programs on Symptoms of Anxiety, Hostility, and Depression in Young and Older Patients with Coronary Artery Disease.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Young Patients (n = 104)</th>
<th>Older Patients (n = 260)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before Rehabilitation</td>
<td>After Rehabilitation</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>$P$ Value</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>27.9</td>
<td>8.7</td>
</tr>
<tr>
<td>Hostility</td>
<td>12.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Depression</td>
<td>23.1</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Data adapted from Lavie et al,\textsuperscript{18} reproduced with permission from Lavie et al.\textsuperscript{1}
Psychosocial Stress

- May trigger acute cardiac events
- Is a significant CAD risk factor
- Forms a barrier to medical interventions
- Is linked to behavioral & cardiovascular risk factors
- Is highly prevalent in cardiac practice
- Commonly masquerades as cardiac symptoms
Adverse Behavioral Factors in Young and Elderly

Baseline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Young (n=104)</th>
<th>Elderly (n=260)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td>23%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>28% *</td>
<td>14%</td>
<td>0.01</td>
</tr>
<tr>
<td>Hostility</td>
<td>13% *</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
A graph showing cumulative hazard over time for different categories of VO₂ loss and gain related to depression status. The table lists the number at risk for each category:

- VO₂ loss/Depressed: 6, 4, 3, 2, 1, 1, 1, 1
- VO₂ gain/Depressed: 8, 7, 6, 4, 3, 3, 1, 1
- VO₂ loss/Non-depressed: 24, 21, 18, 13, 11, 9, 7, 5
- VO₂ gain/Non-depressed: 100, 86, 78, 67, 60, 52, 41, 33
A graph showing the percentage free from clinical event over years of follow-up for different groups: CR + SMT, CR-Alone, and No-CR. The table below lists the number of patients at risk and the years of follow-up for each group:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. at risk</th>
<th>Years of Follow-up</th>
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</thead>
<tbody>
<tr>
<td>Overall</td>
<td>226</td>
<td>111</td>
</tr>
<tr>
<td>CR + SMT</td>
<td>76</td>
<td>49</td>
</tr>
<tr>
<td>CR-Alone</td>
<td>75</td>
<td>37</td>
</tr>
<tr>
<td>No-CR</td>
<td>75</td>
<td>25</td>
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