Posttraumatic Stress Disorder and Cardiovascular Disease

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Abstract

Posttraumatic stress disorder (PTSD) is an anxiety disorder initiated by exposure to a traumatic event and characterized by intrusive thoughts about the event, attempts to avoid reminders of the event, and physiological hyperarousal. In a number of large prospective observational studies, PTSD has been associated with incident cardiovascular disease (CVD) and mortality. Also, in recent years, a number of studies have shown that cardiovascular events can themselves cause PTSD in more than 1 in 8 patients with acute coronary syndrome. Further, a few small studies suggest that PTSD secondary to an acute CVD event then places patients at increased risk for subsequent CVD events and mortality. In this article, we review the evidence for a link between PTSD and CVD, and discuss potential mechanisms for that association as well as future directions for research.

PTSD and risk for incident CVD/mortality

In recent years, evidence has accumulated that PTSD due to various types of traumatic experiences, including exposure to combat, the World Trade Center attacks, and other similar life-threatening events is associated with development of cardiovascular disease, acute coronary syndromes, and cardiac-specific mortality. To date, 5 prospective cohort
studies (with a total of 401,712 participants) have estimated the association of PTSD with incident CVD and/or mortality. Those studies adjusted for numerous demographic, clinical, and psychosocial factors including depression, and followed participants from 1 to 30 years. The effect sizes they reported have ranged from a hazard ratio for incident CVD and/or cardiac mortality of 1.46 to 3.28. Given the consistent findings of these studies on PTSD and CVD, attention has turned to understanding the pathologic mechanisms that connect these two disorders.

**Mechanisms linking PTSD to CVD**

Several studies have found the association of PTSD and CVD to be independent of traditional CVD risk factors, such as hypertension, diabetes, and dyslipidemia. Therefore, we must consider other mechanisms through which PTSD could cause CVD. Though no studies have comprehensively evaluated the mechanisms linking PTSD and CVD, a number of potential mechanisms have been proposed. These can be classified into three categories that will be discussed below: biological, behavioral, and psychosocial risk factors.

**Biological risk factors**

Biological mechanisms of increased CVD risk in PTSD include dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system dysfunction, and increased inflammation. The neurobiology of PTSD is complex, with conflicting reports about basal as well as reactive cortisol levels in patients with PTSD. Overall, studies indicate that the disruption of the HPA axis in patients with PTSD leads to lower basal cortisol secretion, but exaggerated secretion in response to psychological stressors, such as trauma reminders. HPA hyperreactivity, in turn, has been implicated in the development of heart failure and cardiac ischemia and is prospectively associated with increased CVD mortality. Other neuroendocrine alterations observed in PTSD include increased negative feedback sensitivity of glucocorticoid receptors in the stress-response system, decreased glucocorticoid responsiveness, and lower urinary and plasma cortisol levels. Autonomic balance may also be altered, as evidenced by an exaggerated catecholamine response to stressful circumstances and higher concentrations of circulating catecholamines. Alterations in these pathways may lead to CVD via increases in blood pressure and coagulation, as elevated catecholamines have direct effects on the heart, blood vessels, and platelets. Catecholamines have also been implicated in the development of heart failure and cardiac ischemia. In addition, patients with PTSD demonstrate decreased heart rate variability, baroreflex dysfunction, and increased QT variability on electrocardiograms. Each of these physiologic measures has been linked to CVD risk, as reduced heart rate variability predicts mortality after myocardial infarction, reduced baroreflex sensitivity has been linked with carotid atherosclerosis and increased risk of CVD, and increased QT variability is a predictor of sudden cardiac death. Inflammation is another important potential mechanism of increased CVD risk. Though increases in inflammatory cytokines can be adaptive in the setting of repair of acute injury, chronic inflammation is now recognized to be a major factor in the pathogenesis and progression of cardiovascular disease. von Känel and colleagues found a dose-response relationship between severity of PTSD symptoms and inflammation, including increased levels of tumor necrosis factor α and interleukin 1β and decreased levels of the anti-inflammatory cytokine interleukin 4. Several other studies of PTSD and inflammation have reported conflicting results, potentially due to small sample sizes and variations in measurements. However, a recent systematic review confirmed that the majority of studies demonstrated patients with PTSD had higher levels of inflammation. Finally, as studies shed light on the genetics of PTSD, we may find shared variance in susceptibility to PTSD and CVD or its risk factors.
Behavioral risk factors

Potential behavioral mediators of increased CVD risk include substance use, obesity, decreased physical activity, medication nonadherence, and sleep disturbance. Patients with PTSD are known to have higher rates of tobacco use and alcohol and substance dependence even when compared to trauma-exposed controls, and use and dependence may be related to self-medication of anxiety and hyperarousal symptoms.\textsuperscript{31,32} Patients with PTSD also face added challenges when attempting to reduce substance use. For example, in a study of tobacco cessation, those with PTSD experienced significantly greater withdrawal symptoms and urges to smoke after overnight abstinence.\textsuperscript{33} PTSD has also been associated with a substantially increased risk of obesity in large epidemiologic studies as well as a national study of administrative data from younger veterans.\textsuperscript{34,35} This association is likely multifactorial and could involve several other lifestyle factors, such as poor diet and decreased physical activity. Though little data has been published on dietary intake in patients with PTSD, multiple studies, including one conducted in patients with existing CVD, have found patients with PTSD report lower rates of physical activity.\textsuperscript{36,37} Sedentary behavior may be particularly important as it is strongly connected to other cardiac risk factors, such as increased blood pressure, insulin resistance, and cholesterol levels.\textsuperscript{38}

Beyond these lifestyle factors, we and others have shown that PTSD is associated with nonadherence to prescribed medications, another predictor of CVD events.\textsuperscript{39,40} Finally, patients with PTSD experience numerous sleep disturbances, including nightmares, difficulty falling/staying asleep, and sleep disordered breathing.\textsuperscript{41} These sleep disturbances may result from increased release of corticotropin releasing hormone and other mediators of anxious arousal in the brain.\textsuperscript{42} In addition to being distressing for the patient, such sleep disturbances are now recognized as important risk factors for the development and progression of CVD.\textsuperscript{43,44}

Psychosocial risk factors

Comorbid psychological disorders and impairments in social functioning may also increase CVD risk in patients with PTSD. Though the association between PTSD and CVD has remained significant after adjustment for depression in several studies, depression remains a strong risk factor for CVD and could further increase risk of cardiac events when present.\textsuperscript{45} A recent meta-analysis of 39 studies also found strong associations between PTSD and anger and hostility.\textsuperscript{46} Higher levels of anger and hostility, in turn, are associated with significant increases in anginal symptoms, myocardial infarction, and angiographic severity of CVD.\textsuperscript{47}

In addition to these psychological risk factors, the avoidance symptoms present in PTSD can lead to difficulties with developing and maintaining relationships that may decrease social networks and support. In a community-based study of 2,985 adults, those with PTSD reported significantly lower levels of social support and greater social phobia.\textsuperscript{48} Social isolation has been linked to decreased survival following myocardial infarction and to higher total mortality.\textsuperscript{49} Lastly, PTSD is associated with emotional and physical disabilities that can decrease socioeconomic status. In the National Comorbidity Survey, a population-based study of U.S. adults, participants with PTSD had a 40% increased likelihood of not completing high school or college and a 150% increased likelihood of current unemployment compared to participants without PTSD. Socioeconomic status is strongly associated with an increased risk of CVD events and mortality independent of traditional CVD risk factors and access to healthcare.\textsuperscript{50}
Possible interventions to reduce CVD risk

Though we may not be able to prevent people from being exposed to traumatic events or from developing PTSD, this should not deter us from viewing PTSD as an important, modifiable CVD risk factor. Unfortunately, despite the high prevalence of trauma and PTSD and the existence of brief, validated screening tools, PTSD is often not assessed in medical care settings. A nationally representative survey of US adults also found that only 7% of patients with PTSD received treatment within the first year after symptom onset and the median time between initial symptoms and treatment was 12.1 years. Recognition of damaging downstream consequences, such as increased CVD risk, may help improve awareness of PTSD and adoption of PTSD screening and treatment programs that can reduce delays to receiving care.

To date, no study has tested whether PTSD treatment can reduce risk for incident CVD or has evaluated other specific methods of decreasing CVD risk in patients with PTSD. Therefore, at present, the most widely offered strategy for offsetting the CVD risk associated with PTSD due to traumatic events has been increased screening for and treatment of PTSD with concomitant screening for CVD risk factors to initiate early interventions for CVD risk factor control. Although improvements in traditional CVD risk factors are likely to be beneficial, as described above, these factors explain only a modest portion of the CVD risk associated with PTSD. Therefore, we must develop a better understanding of the mechanisms linking PTSD and CVD in order to design targeted interventions to reduce cardiovascular events and mortality in patients with PTSD.

Fortunately, multiple trials have demonstrated that the potential mediators described above can be improved with behavioral and pharmacologic therapies. For example, pro-inflammatory biomarkers such as interleukin-6 and C-reactive protein decrease in response to exercise interventions. Treatment with statins also reduces inflammatory biomarker levels and adverse CVD outcomes. In addition, several studies have successfully targeted behavioral risk factor reduction to patients in PTSD. For example, integration of tobacco cessation counseling in mental health care significantly improved abstinence over an 18 month period in patients with PTSD, and both prazosin and cognitive behavioral therapy have demonstrated efficacy for sleep disturbances in PTSD. As research continues to identify which of these mechanisms are most important and therefore promising for targeted CVD risk reduction, ongoing trials of pharmacologic and behavioral treatments for PTSD could examine the direct effects of PTSD symptom reduction on these potential mechanisms.

PTSD due to cardiovascular events

While PTSD is widely considered a disorder of combat veterans and sexual assault survivors, in the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition; DSMIV), life-threatening medical illness is recognized as an event that can elicit PTSD. In the nearly 20 years since that expansion of the PTSD diagnostic criteria to include life-threatening illness, a large body of research has documented substantial rates of PTSD due to cancer, acute coronary syndromes (ACS), and stroke. Because of the relative homogeneity of the type of traumatic event that induces PTSD symptoms within ACS and stroke patient populations, the elevated recurrent CVD risk endemic to those populations, and the existence of a few strong cohort studies of survivors of CVD events, we have gained substantial knowledge about the prevalence of PTSD due to CVD, its association with CVD recurrence risk and mortality, and potential mechanisms by which that risk is carried.
1. Prevalence of PTSD due to acute coronary syndromes

In a systematic review and meta-analysis of 24 studies (N = 2383), we sought to determine the prevalence of PTSD after ACS. Our pooled estimate for the prevalence of ACS-induced PTSD was 12%, however, estimates of the prevalence of PTSD varied widely. That variability may be due to a number of sampling and research design decisions or may reflect some true demographic, clinical, or geographic variability in the susceptibility of ACS patients to PTSD.

Positive screen versus diagnosis

In any discussion of the prevalence of a psychiatric disorder, the method for determining cases will partially dictate the prevalence estimate. In most of the extant studies of ACS-induced PTSD, researchers have relied on self-report screening instruments. Many of those instruments have good to excellent agreement with clinical diagnosis, but the level of agreement depends on the use of an appropriate cutoff score, which may vary depending on sample characteristics. A few studies have employed clinicians to conduct full clinical diagnostic interviews for ACS-induced PTSD. In our meta-analysis of the prevalence of ACS-induced PTSD, we found that the aggregate estimate of the 17 studies in which patients were assessed solely with screening questionnaires was 16% (95% CI, 13%–20%), compared with 4% in the 7 studies in which patients were assessed with clinical interviews (95% CI, 3%–5%). While the discrepancy between these estimates may be important for patients’ quality of life and psychiatric treatment decisions, studies that have found increased risk for subsequent ACS and mortality associated with PTSD symptoms have all relied on screening questionnaires, suggesting that the 16% of ACS patients with elevated symptoms are at increased risk for adverse outcomes.

Study factors associated with PTSD prevalence

Across the 24 studies that have assessed ACS-induced PTSD, prevalence estimates varied from 0%–32%. However, the largest of the studies included 394 participants, and all of the studies were in fairly homogenous samples (in terms of race/ethnicity/socioeconomic status/culture/nationality), suggesting that no individual estimate is particularly representative of the population from which it was drawn and certainly not representative of the population of all ACS survivors. We found that studies comprised of younger participants tended to have higher rates of ACS-induced PTSD, a phenomenon that is reflected in patient-level PTSD prediction models across studies of PTSD due to life threatening illness. Younger ACS survivors may view their ACS event as particularly threatening because it may be among their first major illnesses, and they have seen fewer of their peers experience such events.

Patient-level factors associated with PTSD risk

Patient-level risk factors for ACS-induced PTSD include intense fear, perceived life threat, lack of control, helplessness, chest pain, and/or dissociation during the ACS event, acute stress disorder and/or depression symptoms during hospitalization, history of psychiatric disorder prior to ACS, alexithymia, and neuroticism. It is important to note that most people who experience life threatening events respond with some degree of fear and psychological distress, but extreme distress during the event defines that event as traumatic and is a potent predictor of future PTSD. Demographic factors associated with ACS-induced PTSD in some studies include younger age, female sex, ethnic minority status, and low socioeconomic status. While these scattered risk factor studies have been useful, a unified risk stratification strategy is warranted for predicting which patients are most likely to develop ACS-induced PTSD. It is important to note that objective clinical severity of the ACS event is not associated with ACS-induced PTSD, either at the study level or at the patient-level, a fact that tends to reinforce the common belief that personality...
factors, previous psychiatric history, and other individual patient traits fully determine which patients will develop ACS-induced PTSD. However, recent research suggests that external factors during ACS treatment can also significantly influence the development of ACS-induced PTSD symptoms.

**Treatment factors and risk for PTSD**

The experience of an ACS is probably universally frightening to some degree, but in order for an individual to develop PTSD, a life threatening event generally must induce feelings of intense fear, helplessness, and/or horror (though the diagnostic criteria for PTSD may soon disregard the requirement that patients report these subjective feelings). Since a major component of the experience of an ACS occurs in emergency departments (ED) and catheterization labs, we recently tested the hypothesis that more stressful medical environments increase the likelihood of developing PTSD after an ACS. We recorded the initial triage time of each of 135 ACS patients, estimated the degree of ED crowding they experienced, and then assessed their ACS-induced PTSD symptoms 1 month later. We divided the ED crowding variable into tertiles, and found that for every tertile increase in ED crowding, participants experienced a 2.5 point increase in PTSD score, after adjustment for a number of demographic, clinical, and psychiatric covariates. It may be the case that pre-existing person-level factors may exacerbate individual patients’ responses to ED crowding, but our results suggest an independent effect of ED crowding on the development of ACS-induced PTSD. Interestingly, while symptoms of depression at the time of the ACS are patient-level predictors of subsequent development of PTSD, the presence of depression symptoms during ED treatment does not influence the association of ED crowding to the development of PTSD symptoms.

**Course of PTSD over time**

For some of the same reasons that we are unsure of the true prevalence of ACS-induced PTSD, the true course of PTSD symptoms is unknown, and is likely influenced by a number of demographic, clinical, and psychosocial factors. Wikman and colleagues found that 12% of 213 participants screened positive for ACS-induced PTSD at 12 months post-ACS, and that 12.8% of 179 of those participants screened positive for ACS-induced PTSD at 36 months. However, while PTSD symptoms were relatively stable, there were participants who screened positive at 12 months who did not at 36 months, and vice versa, as 63% of the variance in 36 month PTSD symptoms were explained by 12 month PTSD symptoms. Ginzburg and colleagues published the longest follow-up of ACS patients with measurement of ACS-induced PTSD, with multiple measurements of PTSD symptoms over multiple years. They found that participants generally were able to be categorized into a large resilient group who experience some psychological distress in the first 7 months after the ACS but recover, and a much smaller group of about 6% of participants who still had significant ACS-induced PTSD symptoms 8 years later.

**Future directions**

A number of studies have now shown that ACS-induced PTSD is relatively common, but a great deal of variability exists across individual study prevalence estimates. A large national study would not only give a more precise estimate of the prevalence of ACS-induced PTSD, but would also offer an opportunity to tease out geographical and socioeconomic variables from race/ethnicity and other person-level predictors toward a PTSD risk prediction tool similar to a Framingham or GRACE score, but instead for the prediction of ACS-induced PTSD. Perhaps more important, though, is the possibility that there are modifiable factors that occur during the course of ACS care that may influence the development of PTSD symptoms, such as ED crowding. Future research should further elucidate those factors and the mechanisms by which they may influence PTSD toward the development of...
organizational interventions to reduce ACS-induced PTSD incidence. In the meantime, we know that 1 in 8 ACS patients are developing ACS-induced PTSD, but only one small treatment study exists that was not powered to detect even large effect sizes. This small study did suggest that ACS-induced PTSD treatment is safe and promising.\textsuperscript{96} Aside from the quality of life benefits that would likely attend successful ACS-induced PTSD treatment, such treatment may also offset secondary ACS recurrence and mortality risk in ACS patients.

2. Association of ACS-induced PTSD to ACS recurrence/mortality

In the same article in which we estimated the prevalence of ACS-induced PTSD from 24 studies, we used meta-analysis to estimate the effect size of the association between ACS-induced PTSD and risk of adverse outcome based on estimates provided by the 3 studies that prospectively assessed this association. The first study to assess the association of ACS-induced PTSD to cardiac rehospitalization was Shemesh and colleagues\textsuperscript{97} study in 73 ACS patients followed for 1 year post-ACS, but that study did not adjust for potential confounders of the association including demographics, disease severity, or depression.

Seven years later, two other studies documented an association between ACS-induced PTSD and ACS recurrence and/or mortality. Edmondson and colleagues\textsuperscript{73} measured ACS-induced PTSD symptoms 1 month post-ACS in 247 participants, then followed them for 42 months to ACS recurrence or mortality. The unadjusted hazard ratio (HR) associated with a positive screen for PTSD was 2.42 (95% CI, 1.1–5.4), but after adjustment for sociodemographic and clinical disease severity, the HR for positive ACS-induced PTSD screen was attenuated to 2.04 (95% CI, 0.9–4.9). After further adjustment for depression symptoms during hospitalization, the HR was further attenuated to 1.36 (95% CI, 0.5–3.5). However, when the three symptom clusters of PTSD (reexperiencing, avoidance, and hyperarousal) were considered separately in the fully adjusted model, participants who reported high levels of reexperiencing symptoms (i.e., intrusive thoughts, nightmares) were at significantly greater risk for ACS recurrence and mortality, HR= 3.35 (95% CI, 1.3–8.8). Similarly, von Kanel and colleagues\textsuperscript{98} found that risk for ACS recurrence increased with each 10 point increase in ACS-induced PTSD symptoms (measured around 3 months post-ACS), with a HR of 1.42 (95% CI, 1.1–1.9).

By combining the three estimates, we found that a positive screen for ACS-induced PTSD is associated with an approximate doubling of the risk of adverse medical outcomes, even after adjusting for depression and other important covariates (adjusted hazard ratio HR, 2.0; 95% CI, 1.7–2.4).\textsuperscript{72} It is important to note that each of these studies used a cutoff on an ACS-induced PTSD symptom questionnaire rather than a clinical interview to classify PTSD status, suggesting that the larger of the two prevalence estimates—the estimate based on self-report screening instruments—is the estimate that is most important in terms of possible ACS recurrence risk stratification based on PTSD status. As such, if the aggregate prevalence estimate based on extant studies of ACS-induced PTSD is valid, we expect that about 16% of ACS patients develop PTSD symptoms severe enough to place them at increased ACS recurrence or mortality risk.

3. Mechanisms

Many of the mechanisms that have been proposed to explain the association between ACS-induced PTSD and adverse outcomes are the same as those proposed to explain the association of PTSD to incident CVD. However, whereas the average length of follow-up for studies that have shown an association of PTSD to incident CVD is almost 10 years, ACS-induced PTSD seems to increase risk for recurrent ACS and mortality within a few months or years. As such, either the mechanisms that are thought to exert long-term
cumulative effects on the cardiovascular system work more quickly in post-ACS patients, or the more short-acting mechanisms are the most likely candidates for mediators of the ACS-induced PTSD to ACS recurrence/mortality association.

### Physiological risk factors more pronounced in ACS-induced PTSD

We know that both ACS and PTSD are associated with sympathetic activation and elevated proinflammatory cytokines, including C-reactive protein \(^99\), tumor necrosis factor, and interleukin 1 \(^99\). It is likely that the additive effects of the inflammation found in patients with PTSD may adversely affect recurrence risk.\(^{100}\) Recently, Ahmadi and colleagues\(^{101}\) showed that PTSD is associated with mortality more strongly at higher levels of coronary artery calcium, suggesting that PTSD may exert greater influence on secondary risk than primary risk.

### Behavioral risk factors

Among the behavioral risk factors mentioned above, the two most likely candidates for mechanisms of the ACS-induced PTSD-secondary risk association are medication nonadherence and sleep disruption. While the small Shemesh\(^97\) study discussed above could not adjust for important covariates in the PTSD to rehospitalization association, it did show that participants who screened positive for ACS-induced PTSD were more likely to show evidence of nonadherence to aspirin in the months after their index ACS. Medication nonadherence may exacerbate many of the physiological mechanisms that have been proposed. Sleep difficulties are a common feature of PTSD,\(^{41}\) and are also a common complaint after ACS.\(^{102,103}\) While sleep difficulties have been shown to be associated with CVD events,\(^{44}\) no study has yet tested poor sleep as a mediator of the association of ACS-induced PTSD and adverse CVD outcomes.

### Prevalence of PTSD due to stroke

While most studies of the relationship between PTSD and cardiovascular disease have focused on the potential for PTSD due to ACS, a few studies have assessed stroke-induced PTSD. Across the eight extant studies, prevalence estimates vary widely from 3% to 37%.\(^{79,81,83,84,104–106}\) Moreover, most of those studies relied on small samples assessed at various lengths of time after the index stroke. Further, most published studies to date were conducted in majority white populations without significant racial or ethnic diversity, although risk for PTSD is greater in black survivors of some types of trauma.\(^{107,108}\) Our recent study, the largest on this topic to date, found that 18% of 535 survivors of mild to moderate stroke reported clinically significant PTSD symptoms a mean ± SD of 1.9 ± 1.5 years later.\(^{80}\) Strikingly, in that study, we found that participants with elevated stroke-induced PTSD symptoms were 2.7 times more likely than those without PTSD symptoms to report medication nonadherence.\(^{80}\) However, the participants in that study were primarily from racial and ethnic minority groups with very low socioeconomic status living in New York City,\(^{109}\) so the generalizability of that result to the broader population of stroke survivors in the United States is unclear.

### Conclusions

Research conducted in the past decade has now accumulated such that we can confidently conclude that an association exists between PTSD and incident CVD, and likely exists between PTSD and recurrent CVD, and that the association is independent of other known risk factors. However, we are not able to point to a single mechanism that can explain that association. That inability likely exists for two reasons: the studies that could pinpoint that mechanism have not been conducted, and the association is carried by multiple mediators.
whose relative effects are contingent upon individual patient factors. Future research should focus on (1) methods for decreasing PTSD, particularly where medical settings can be modified to decrease PTSD due to ACS, stroke, and other life-threatening medical illnesses, (2) identifying modifiable mechanisms of the association of PTSD and CVD, particularly non-traditional risk factors, and (3) determining whether PTSD treatment can offset CVD risk.

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Abbreviations

| Abbreviation | Description                        |
|--------------|------------------------------------|
| ACS          | acute coronary syndrome            |
| CVD          | cardiovascular disease             |
| ED           | emergency department               |
| HPA          | hypothalamic-pituitary axis        |
| PTSD         | posttraumatic stress disorder      |

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