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Anxiety and Cardiovascular Disease Risk: a Review

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Abstract Unrecognized anxiety is a difficult clinical presentation in cardiology. Anxiety leads to recurring emergency department visits and the need for numerous diagnostic evaluations to rule out cardiovascular disease (CVD). This review focuses broadly on anxiety and its subtypes in relation to the onset and progression of CVD while describing helpful guidelines to better identify and treat anxiety. Potential mechanisms of cardiopathogenesis are also described. An emerging literature demonstrates that anxiety disorders increase the risk for incident CVD but a causal relationship has not been demonstrated. Anxiety portends adverse prognosis in persons with established CVD that is independent from depression. The level of clinical priority received by depression should be extended to research and clinical intervention efforts in anxiety. Anxiety holds direct relevance for uncovering mechanisms of cardiopathogenesis, developing novel therapeutic strategies, and initiating clinical interventions in the population at risk of developing heart disease, or those already diagnosed with CVD.

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Introduction

Anxiety has been implicated in arterial hypertension, coronary heart disease (CHD), and open heart surgery outcomes for more than 100 years [1–3]. Despite the inextricable relevance of anxiety to cardiovascular function and cardiovascular disease (CVD), surprisingly, the etiological and prognostic links between anxiety disorders and CHD are only now emerging. Recent empirical advances point to the strong likelihood that anxiety disorders increase the risk for developing CVDs [4••, 5, 6•, 7, 8••, 9]; however, a causal relationship remains elusive. Likewise, anxiety disorders confer a prognostic risk for subsequent major adverse coronary events (MACE, e.g., myocardial infarction [MI], left ventricular failure, coronary revascularization procedure, and stroke) in persons with established CVDs [10•]. In this review, the epidemiological evidence relating to different anxiety disorders and CVDs is described, while closely examining anxiety disorders' association with clinical outcomes that are pertinent to cardiovascular function. We also describe pharmacological and non-pharmacological treatment approaches in this population.

What Is Anxiety?

Unrecognized anxiety is indeed a troubling clinical presentation for the cardiologist due to recurring emergency department visits and exhaustive diagnostic work-ups to rule out "organic" disease. The cardiologist is especially challenged by anxious patients with persisting cardiovascular symptoms despite conventional medical treatment or the absence of

remarkable diagnostic findings. Further complicating the clinical presentation, anxiety includes a range of cardiorespiratory symptoms reflecting heightened autonomic arousal and may include palpitations, accelerated heart rate, chest pain, dyspnea, dizziness, numbness, and abdominal distress. Other symptoms span the cognitive (e.g., fear, worry, catastrophizing, rumination, thought suppression) and behavioral (avoidance of places or situations, safety seeking behaviors, compulsions) milieus, which appear covertly or may go unnoticed. As such, it is recommended to consider anxiety as a diagnosis only by using the guidelines of the prevailing Diagnostic and Statistical Manual of Mental Disorders [11] or International Classification of Disease Criteria.

In the broadest sense, anxiety disorders described herein focus on panic disorder, generalized anxiety disorder (GAD), social phobia, and specific phobia, but might also refer to agoraphobia and anxiety due to a general medical condition. Along these lines, both the American Heart Association [12] and German Heart Association [13] recommended that further research must strive to identify the independent contribution of anxiety disorders and its subtypes to CVD prognosis.

Anxiety Prevalence in CVD: a Review of Recent Epidemiological Studies

The association between anxiety and CVD is demonstrated in cross-sectional, etiological, and prognostic studies. The prevalence of anxiety disorders is substantially greater in CVD populations than in the general population [14]. Our recent meta-analysis indicated that the point prevalence rate of any anxiety disorders in CVD populations was approximately 16 %. The prevalence rate of GAD and panic disorder is much higher in CVD patients than the general population (Table 1) [10•]. Importantly, anxiety disorders are as common as unipolar depression disorder in the population with acute coronary syndrome (ACS) [15–18] and after coronary artery bypass graft (CABG) surgery [19–22]. Anxiety disorders are comorbid with depression disorders in approximately 50 % of CVD cases [10•], highlighting strong intraindividual comorbidity, which parallels findings in psychiatric and community samples [23–25]. Identifying anxiety-depression disorder comorbidity is particularly important because ACS patients with an anxiety disorder are more likely to have insufficiently treated depression and, in turn, be at higher risk for subsequent MI [26].

There are known caveats to the accuracy of anxiety disorder diagnoses and prevalence estimates in CVD. Anxiety fluctuates over time and is experienced by almost all individuals to some degree. Therefore, single-assessment approaches and short questionnaires can be less reliable when compared to validated diagnostic approaches that take into account longer time periods and lifetime exposure [28]. Anxiety disorder prevalence fluctuates between studies contingent on an in- or out-patient setting, patient age, gender, and whether (or not) examiners are blinded to CHD status [16]. Making an anxiety disorder diagnosis in CVDs is not straightforward and the pitfalls of somatic symptoms confounding a psychiatric diagnosis in chronic diseases are well known [29]. Indeed, the clinical presentation of CVDs and anxiety frequently overlap in the acute setting, especially atypical chest pain, dyspnea, palpitations, and arrhythmias [10•, 30–34]. We highly recommend cardiologists obtain a diagnosis by a structured psychiatric interview or refer to a psychiatrist or psychologist for further assessment.

Does Anxiety Increase CVD Risk? A Review of Etiological and Prognostic Studies

Etiological data highlights the important role of anxiety disorders in CVD. A widely cited meta-analysis [35] explored the association between anxiety and incident CHD across 20

Table 1 Prevalence of common anxiety disorders in the CHD and general population

Disorder	Number of CHD studies in meta-analysis (pooled sample size)	Prevalence in CHD [10•]	95 % CI	Prevalence in general population [27]
Generalized anxiety disorder[a]	22 (5567)	7.97	5.42–11.57	3.1
Panic disorder[a]	29 (4713)	6.81	4.09–11.14	2.7
Agoraphobia[a]	17 (2885)	3.62	1.78–7.21	0.8
Social phobia	10 (1847)	4.62	2.31–9.02	6.8
Specific phobia	11 (1795)	4.31	2.23–8.15	8.7
Obsessive compulsive disorder	6 (1558)	1.80	1.23–2.65	1.0

Data from [10•]

[a] Higher in CHD populations and related to CVD in etiological and prognostic studies

studies and follow-up periods ranging from 2 to 21 years. In initially healthy samples, anxiety (defined as any anxiety, panic, phobia, post-traumatic stress, and worry) was associated with a 26 % increased risk of incident heart disease and 48 % increased risk of cardiac mortality.

Recent studies suggest anxiety is associated with younger age at the time of first MI [36, 37]. Evidence is mixed on possible gender differences in CVD risk though anxiety and depression are more commonly reported among females than males. Walters et al. [36] showed that the incident rate of CHD was consistent among both males and females of all ages in their cohort of more than 400,000 UK residents. More recently, the Hertfordshire cohort study showed a significant association between anxiety and CVD occurrence in men (OR = 1.10, 95 % CI 1.05–1.15) but not women [38].

Anxiety Disorder Subtypes

Analyzing anxiety disorder subtypes has uncovered differential associations with CVD that mainly implicate panic disorder and GAD with etiological and prognostic outcomes, respectively. The discrete role of panic and GAD is highlighted in two recent studies from The Netherlands. Over a 6-year follow-up, CVD incidence was associated with panic disorder (HR = 2.12, 95 % CI 1.27–3.55) in the Netherlands Study of Anxiety and Depression [5]. By contrast, in the NEMESIS study [39], only GAD was associated with non-fatal CVD over 3 years. As such panic and GAD will be primarily described in terms of their respective risk for etiological and prognostic outcomes.

Robust evidence indicates that panic disorder is associated with incident CHD [8••]. Our recent systematic review showed that incident CHD risk in persons with panic disorder was increased by 47 % (hazard ratios are presented in Fig. 1 [8••]). Risk for MI and MACE were increased by 36 and 40 %, respectively.

Our meta-regression according to general study characteristics showed sources of considerable statistical heterogeneity for the incident CHD outcome (refer to Fig. 2) [8••]. The risk of CHD attributable to panic disorder was increased with the percentage of females in a study and was decreased with participant age (both $p < .05$). Adjusting for risk factors of socioeconomic status and diabetes and covariate alcohol consumption were also sources of heterogeneity between studies. This suggests that certain patient- and study-level characteristics influence the association between panic and CHD onset.

Because baseline coronary angiography and cardiology work-up are rarely performed [9], we concluded that reverse causality between CHD and panic disorder could not be ruled out [8••]. That is, given the clear overlap between panic disorder and CHD symptoms, it is plausible that panic disorder may aggravate underlying subclinical CVD or merely indicate an undiagnosed cardiovascular condition. Another more

	Events n	Analysis n	$_{adj}$HR (95% CI)	Weight %
Albert 2005	930	72,359	3.43 (1.27 – 9.26)	2.3
Bowen 2000	153	2,657	1.50 (1.10 – 2.05)	7.6
Bringager 2008	11	167	0.92 (0.29 – 2.92)	1.8
Chen 2009	1,249	33,696	1.62 (1.41 – 1.86)	9.5
Gomez- Camerino 2005	32,995	78,580	1.87 (1.83 – 1.91)	10.1
Jakobsen 2008	1,049	75,861	1.56 (1.35 – 1.80)	9.4
Jansky 2010	1,894	49,321	2.17 (1.28 – 3.68)	5.1
Kawachi 1994	168	33,999	2.66 (0.40 – 17.69)	0.7
Nabi 2010 (females)	209	14,298	1.47 (1.04 – 2.08)	7.1
Nabi 2010 (males)	NS	9,830	1.15 (0.92 – 1.44)	8.6
Rohacek 2010	7	191	0.31 (0.02 – 4.80)	0.4
Scherrer 2010 (PD + MD)	12,304	355,999	1.22 (1.07 – 1.39)	8.3
Scherrer 2010 (PD - MD)	NS	NS	1.43 (1.11 – 1.84)	9.6
Walters 2008 (age <50 yrs)	1,097	275,966	1.44 (1.25 – 1.65)	9.9
Walters 2008 (age >50 yrs)	6,045	128,677	1.11 (1.03 – 1.20)	9.5
Pooled data and effect	**58,111**	**1,131,612**	**1.47 (1.24 – 1.74)**	**100**
P for overall effect			**P<.00001**	**I^2 = 94**

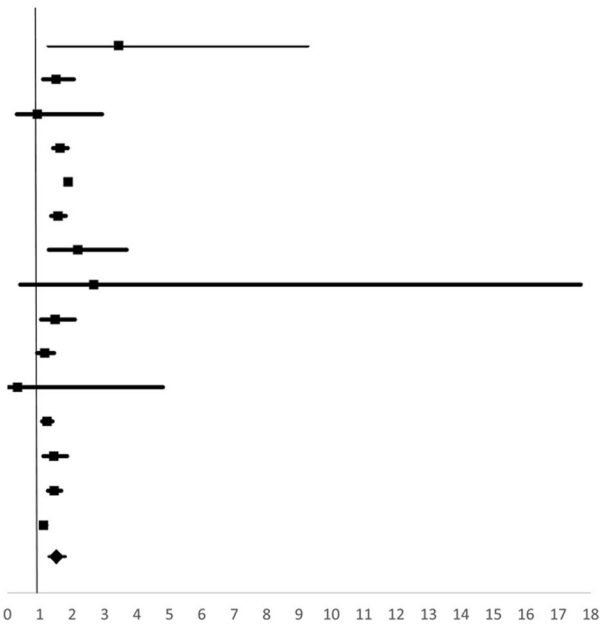

Fig. 1 Forest plot of adjusted and weighted hazard ratios for incident coronary heart disease (CHD) (primary endpoint) in relation to panic disorder. Adjusted hazard ratios ($_{adj}HR$) with 95 % confidence intervals (CI) that exceed 1 (*vertical line*) indicate an increased CHD risk for persons with panic disorder. (From Tully et al. 2015;45(14):2909–20, reproduced with permission from Cambridge University Press) [8••]

Covariate	Events(n)	Analysis(n)	$_{adj}$HR (95% CI)	I^2
Female	5,734	366,119	1.79 (1.44 – 2.23)	62
Male	2,062	83,320	1.56 (0.90 – 2.70)	36
Age < 50	3,044	343,359	1.63 (1.13 - 2.35)	54
Age > 50	6,369	168,732	2.98 (0.53 - 16.68)	99
$_{adj}$Exercise Yes	40,137	483,234	1.44 (1.04 - 2.00)	62
$_{adj}$Exercise No	17,974	648,378	1.47 (1.21 – 1.78)	95
$_{adj}$Tobacco Yes	54,544	912,682	1.42 (1.13 – 1.79)	97
$_{adj}$Tobacco No	3,567	218,930	1.59 (1.44 – 1.74)	0
$_{adj}$Alcohol Yes[a]	21,549	834,102	1.30 (1.15 – 1.46)	68
$_{adj}$Alcohol No[a]	36,562	297,510	1.68 (1.49 - 1.91)	57
$_{adj}$SES Yes[b]	22798	867,798	1.36 (1.19 – 1.55)	79
$_{adj}$SES No[b]	35,313	263,814	1.70 (1.45 – 1.99)	52
$_{adj}$Diabetes Yes[c]	22,798	867,798	1.36 (1.19 – 1.55)	79
$_{adj}$Diabetes No[c]	35,313	263,814	1.70 (1.45 - 1.99)	52
$_{adj}$Cholesterol Yes	53,690	872,929	1.43 (1.12 - 1.82)	98
$_{adj}$Cholesterol No	4,421	258,683	1.48 (1.25 – 1.76)	36
$_{adj}$Hypertension Yes	54,544	912,682	1.42 (1.13 - 1.79)	97
$_{adj}$Hypertension No	3,567	218,930	1.59 (1.44 - 1.74)	0
< 2 Year follow-up[d]	34,419	146,466	1.77 (1.55- 2.02)	48
2-10 Year follow-up[d]	19,819	787,605	1.28 (1.15 - 1.42)	56
>10 Year follow-up[d]	3,873	197,541	1.86 (1.30 – 2.67)	44
North America	46,550	543,594	1.58 (1.22 – 2.05)	89
Europe	10,312	554,322	1.35 (1.15 - 1.60)	76
Asia	1,249	33,696	1.62 (1.41 – 1.86)	0

a. p = .003; b. p = .03; c. p = .033; d. p <.001

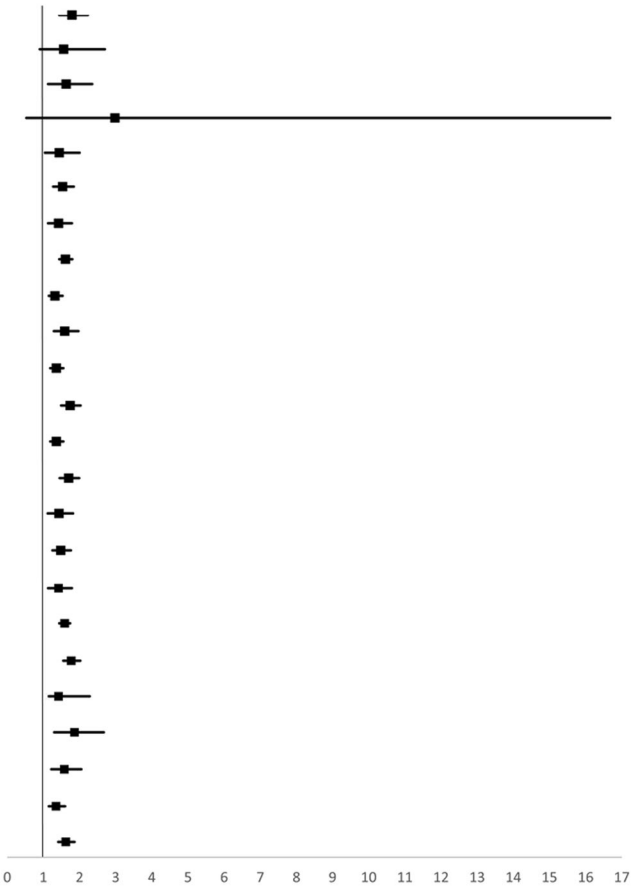

Fig. 2 Adjusted hazard ratios ($_{adj}HR$) for incident coronary heart disease (CHD) and panic disorder (PD) study characteristics, where 95 % confidence intervals (*95 % CI*) exceeding 1 (*vertical line*) represent increased CHD risk for persons with PD. *SES* socioeconomic status. (From Tully et al. 2015;45(14):2909–20, reproduced with permission from Cambridge University Press) [8••]

recent systematic review argued in favor of causality whereby anxiety causes CVD [40•]. Specifically, the authors compared anxiety studies against criteria for causality (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy) and elevated anxiety to causal CVD risk factor status.

Robust prognostic evidence also demonstrates an association between GAD and poorer CVD prognosis in persons with established CHD or heart failure. GAD was associated with adverse CVD and cerebrovascular outcomes at follow-up after CABG surgery (HR] = 2.79, 95 % CI 1.00–7.80) [41]. GAD increased MACE risk approximately twofold in ACS outpatients (n = 804) over 2 years [42]. This association was subsequently corroborated in a large CHD outpatient sample of more than 900 patients [43]. Over the mean 5.6-year follow-up, GAD was associated with an increase of 74 % in MACE

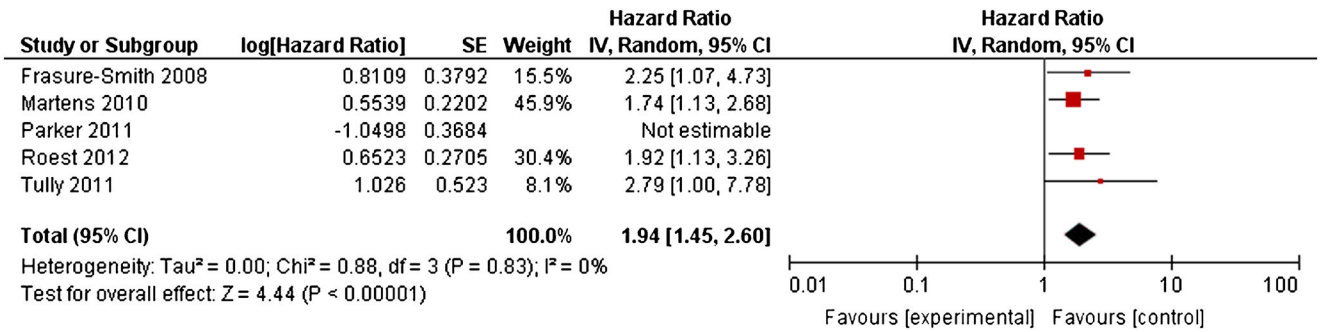

Fig. 3 Major adverse cardiac event risk in generalized anxiety disorder outpatient studies adjusted for covariates (random effects). The figure shows the hazard ratio for major adverse cardiac events in outpatients with generalized anxiety disorder versus persons without generalized anxiety disorder. (From Tully et al. 2014;77(6):439–48, reproduced with permission from Elsevier) [10•]

risk. More recent studies [41, 44–46] confirm the role of GAD in adverse CVD prognosis and these were pooled together in a recent meta-analysis (Fig. 3). Collectively, the findings demonstrate that GAD, independent of depression, increases MACE risk.

Mechanisms of Cardiopathogenesis

Given the breadth in anxiety disorder phenotypes, there is a very wide scope for identifying correlates of cardiovascular function and cardiopathogenesis [47, 48]. Distinction between anxiety subtypes is imperative in order to identify potentially unique mechanisms of cardiopathogenesis that might be hidden on the "any anxiety disorder" group level [49]. Mechanisms of cardiopathogenesis are lesser known than depression but are most consistently demonstrated in panic disorder and GAD. Likely risk factors include hypertension, low ω-3 fatty acid levels, tobacco use, sedentary activity, low medication adherence, inflammatory response, and reduced heart rate variability [43, 44, 50–53]. With regard to the latter, diminished heart rate variability, reflecting impaired vagal function and inflammatory dysregulation, is associated with GAD, panic disorder, and social anxiety disorder [54••]. The mechanisms of cardiopathogenesis attributable to anxiety disorders have also been highlighted in higher levels of creatinine kinase, higher intraoperative glucose levels, and the fewer grafts received by CABG patients with an anxiety disorder [55].

Etiological and prognostic effects relevant to panic disorder are controversial given the disputed causal status of panic disorder [56, 57]. Recent evidence highlights the possible role of biobehavioral cardiopathogenic mechanisms. Behavioral factors of panic that may increase CVD risk include high smoking and nicotine dependence rates [58], alcohol use [59], and avoidance of exercise attributed to fear of exacerbating symptoms [60]. Monitoring studies also suggest panic is associated with myocardial ischemia [61, 62], change in the QT interval [63–65], coronary slow-flow [66], microvascular angina [67], and arterial stiffness [68]. Taken together, evidence indicates several possible mechanisms of cardiopathogenesis but these are poorly understood and warrant further examination.

Anxiety Intervention in CVD

Given that anxiety disorders are common and represent a considerable burden on quality of life [28], focused attention towards treating anxiety may improve daily functioning, delay the onset of CVD and reduce morbidity burden. Several clinical guidelines recommend selective serotonin reuptake inhibitors (SSRIs) for the treatment of various anxiety disorders [69, 70]. The SSRIs have known pleitropic antiplatelet properties, but research also demonstrates SSRIs such as escitalopram prolongs the QTc interval and should not be prescribed at doses higher than 40 mg/day. Other pharmacological treatments such as benzodiazepines are typically used for free-floating anxiety, and SSRIs remain the first-line pharmacological treatment of choice in CVDs [71].

Cognitive behavioral therapy (CBT) is a frontline treatment option for anxiety. In established CVD populations, anxiety intervention is challenging because somatic symptoms of cardiorespiratory origin pose a high risk if medical attention is delayed [72]. Consequently, standard CBT requires considerable adaptation to incorporate this element of risk. Also, certain interoceptive symptom induction experiments may potentiate arrhythmia or myocardial ischemia and are therefore not recommended. To overcome some of these clinical challenges and rectify the absence of empirical treatments, we recently developed a protocol for Panic Attack Treatment in Comorbid Heart Diseases (PATCHD) [73•]. We showed a significant reduction in CVD hospital admissions and length of stay, panic attacks, general anxiety, and depression (all $p < .05$). Otherwise, ongoing trials of anxiety disorder treatment are underway which may provide directions for clinical treatments [74, 75].

Unfortunately, there is no robust evidence to suggest that psychological or pharmacological intervention of depression has an enduring effect on MACE reduction [76–78]. The collective findings indicate that a focus on depression has limited effects on CVD prognosis to date and raise the possibility that interventions must also treat anxiety to improve CVD outcomes [79].

Conclusions

Anxiety disorders are of direct clinical importance to the cardiologist. A consistent body of literature demonstrates a high prevalence of anxiety disorders in CVD that increases the risk for poor cardiovascular outcomes, highlighting that attention should be placed on anxiety disorders in clinical practice and intervention. Future work needs to examine anxiety subtypes in greater detail as cardiopathogenesis data remain limited and causality remains unproven.

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Compliance with Ethical Standards

Conflict of Interest Phillip J. Tully, Nathan J. Harrison, Peter Cheung, and Suzanne Cosh declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Miles HHW, Cobb S. Neurocirculatory asthenia, anxiety and neurosis. New Engl J Med. 1951;245(10):711–9. doi:10.1056/NEJM195111082451901.
2. Fish F. The psychiatric aspects of paroxysmal tachycardia. Br J Psychiatry. 1964;110(1):205–10.
3. Weiss E, Dolin B, Rollin HR, Fischer HK, Bepler CR. Emotional factors in coronary occlusion. I. Introduction and general summary. Arch Intern Med. 1957;99(4):628–41.
4.•• Garfield LD, Scherrer JF, Hauptman PJ, Freedland KE, Chrusciel T, Balasubramanian S, et al. Association of anxiety disorders and depression with incident heart failure. Psychosom Med. 2014;76(2):128–36. doi:10.1097/psy.0000000000000027. **First study to highlight that anxiety disorders increase the risk for incident heart failure**.
5. Seldenrijk A, Vogelzangs N, Batelaan NM, Wieman I, van Schaik DJ, Penninx BJ. Depression, anxiety and 6-year risk of cardiovascular disease. J Psychosom Res. 2015;78(2):123–9. doi:10.1016/j.jpsychores.2014.10.007.
6.• Scott KM, de Jonge P, Alonso J, Viana MC, Liu Z, O'Neill S, et al. Associations between DSM-IV mental disorders and subsequent heart disease onset: beyond depression. Int J Cardiol. 2013;168(6):5293–9. doi:10.1016/j.ijcard.2013.08.012. **The World Health Survey demonstrated that anxiety disorders were associated with higher heart disease risk than depression disorders**.
7. Nabi H, Hall M, Koskenvuo M, Singh-Manoux A, Oksanen T, Suominen S, et al. Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study. Biol Psychiatry. 2010;67(4):378–85. doi:10.1016/j.biopsych.2009.07.040.
8.•• Tully PJ, Turnbull DA, Beltrame J, Horowitz J, Cosh S, Baumeister H, et al. Panic disorder and incident coronary heart disease: a systematic review and meta-regression in 1 131 612 persons and 58 111 cardiac events. Psychol Med. 2015;45(14):2909–20. doi:10.1017/S0033291715000963. **Our large meta-analysis highlights PD as an independent risk factor for incident CHD, MI and MACE**.
9. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. J Am Coll Cardiol. 2010;56(1):31–7. doi:10.1016/j.jacc.2010.03.033.
10.• Tully PJ, Cosh SM, Baumeister H. The anxious heart in whose mind? A systematic review and meta-regression of factors associated with anxiety disorder diagnosis, treatment and morbidity risk in coronary heart disease. J Psychosom Res. 2014;77(6):439–48. doi:10.1016/j.jpsychores.2014.10.001. **Reports prognostic associations between anxiety disorder subtypes and MACE. Important anxiety disorder prevalence data in CHD and treatment approaches are also highlighted**.
11. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? Depress Anxiety. 2009;26(12):1066–85.
12. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association. Circulation. 2014;129(12):1350–69. doi:10.1161/cir.0000000000000019.
13. Ladwig KH, Lederbogen F, Albus C, Angermann C, Borggrefe M, Fischer D, et al. Position paper on the importance of psychosocial factors in cardiology: update 2013. Ger Med Sci. 2014;12:Doc09. doi:10.3205/000194.
14. Todaro JF, Shen BJ, Raffa SD, Tilkemeier PL, Niaura R. Prevalence of anxiety disorders in men and women with established coronary heart disease. J Cardiopulm Rehabil Prev. 2007;27(2):86–91. doi:10.1097/01.HCR.0000265036.24157.e7.
15. Thombs BD, Roseman M, Coyne JC, de Jonge P, Delisle VC, Arthurs E, et al. Does evidence support the American Heart Association's recommendation to screen patients for depression in cardiovascular care? An updated systematic review. PLoS ONE. 2013;8(1), e52654. doi:10.1371/journal.pone.0052654.
16. Di Benedetto M, Lindner H, Hare DL, Kent S. Depression following acute coronary syndromes: a comparison between the Cardiac Depression Scale and the Beck Depression Inventory II. J Psychosom Res. 2006;60(1):13–20. doi:10.1016/j.jpsychores.2005.06.003.
17. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. Am J Psychiatry. 2009;166(4):410–7.
18. Marchesi C, Ossola P, Scagnelli F, Paglia F, Aprile S, Monici A, et al. Type D personality in never-depressed patients and the development of major and minor depression after acute coronary syndrome. J Affect Disord. 2014;155:194–9. doi:10.1016/j.jad.2013.10.052.
19. Tully PJ, Baker RA. Depression, anxiety, and cardiac morbidity outcomes after coronary artery bypass surgery: a contemporary and practical review. J Geriatr Cardiol. 2012;9(2):197–208. doi:10.3724/SP.J.1263.2011.12221.
20. Rafanelli C, Roncuzzi R, Milaneschi Y. Minor depression as a cardiac risk factor after coronary artery bypass surgery. Psychosomatics. 2006;47(4):289–95. doi:10.1176/appi.psy.47.4.289.
21. Dao TK, Youssef NA, Armsworth M, Wear E, Papathopoulos KN, Gopaldas R. Randomized controlled trial of brief cognitive behavioral intervention for depression and anxiety symptoms preoperatively in patients undergoing coronary artery bypass graft surgery. J Thorac Cardiovasc Surg. 2011;142(3):e109–15.
22. Mitchell RH, Robertson E, Harvey PJ, Nolan R, Rodin G, Romans S, et al. Sex differences in depression after coronary artery bypass graft surgery. Am Heart J. 2005;150(5):1017–25.
23. Dilsaver SC, Akiskal HS, Akiskal KK, Benazzi F. Dose-response relationship between number of comorbid anxiety disorders in adolescent bipolar/unipolar disorders, and psychosis, suicidality, substance abuse and familiality. J Affect Disord. 2006;96(3):249–58.
24. Simon NM, Smoller JW, Fava M, Sachs G, Racette SR, Perlis R, et al. Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. J Psychiatr Res. 2003;37(3):187–92.
25. Watson D. Differentiating the mood and anxiety disorders: a quadripartite model. Annu Rev Clin Psychol. 2009;5:221–47.
26. Scherrer JF, Chrusciel T, Garfield LD, Freedland KE, Carney RM, Hauptman PJ, et al. Treatment-resistant and insufficiently treated depression and all-cause mortality following myocardial infarction. Br J Psychiatry. 2012;200(2):137–42. doi:10.1192/bjp.bp.111.096479.

27. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62(6):617–27.
28. Cohen BE, Edmondson D, Kronish IM. State of the art review: depression, stress, anxiety, and cardiovascular disease. Am J Hypertens. 2015;28(11):1295–302. doi:10.1093/ajh/hpv047.
29. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. Gen Hosp Psychiatry. 2007;29(2):147–55.
30. Barsky AJ, Delamater BA, Clancy SA, Antman EM, Ahern DK. Somatized psychiatric disorder presenting as palpitations. Arch Intern Med. 1996;156(10):1102–8.
31. Barsky AJ, Cleary PD, Sarnie MK, Ruskin JN. Panic disorder, palpitations, and the awareness of cardiac activity. J Nerv Ment Dis. 1994;182(2):63–71.
32. Fleet RP, Dupuis G, Marchand A, Burelle D, Beitman BD. Detecting panic disorder in emergency department chest pain patients: a validated model to improve recognition. Ann Behav Med. 1997;19(2):124–31.
33. Fleet RP, Dupuis G, Marchand A, Kaczorowski J, Burelle D, Arsenault A, et al. Panic disorder in coronary artery disease patients with noncardiac chest pain. J Psychosom Res. 1998;44(1):81–90.
34. Tully PJ, Bennetts JS, Baker RA, McGavigan AD, Turnbull DA, Winefield HR. Anxiety, depression, and stress as risk factors for atrial fibrillation after cardiac surgery. Heart Lung. 2011;40(1):4–11.
35. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56(1):38–46. doi:10.1016/j.jacc.2010.03.034.
36. Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. Eur Heart J. 2008;29(24):2981–8. doi:10.1093/eurheartj/ehn477.
37. Mathur R, Perez-Pinar M, Foguet-Boreu Q, Ayis S, Ayerbe L. Risk of incident cardiovascular events amongst individuals with anxiety and depression: a prospective cohort study in the east London primary care database. J Affect Disord. 2016;206:41–7. doi:10.1016/j.jad.2016.07.046.
38. Holt RI, Phillips DI, Jameson KA, Cooper C, Dennison EM, Peveler RC, et al. The relationship between depression, anxiety and cardiovascular disease: findings from the Hertfordshire Cohort Study. J Affect Disord. 2013;150(1):84–90. doi:10.1016/j.jad.2013.02.026.
39. Batelaan NM, ten Have M, van Balkom AJ, Tuithof M, de Graaf R. Anxiety disorders and onset of cardiovascular disease: the differential impact of panic, phobias and worry. J Anxiety Disord. 2014;28(2):252–8. doi:10.1016/j.janxdis.2013.12.003.
40.• Batelaan NM, Seldenrijk A, Bot M, van Balkom AJ, Penninx BW. Anxiety and new onset of cardiovascular disease: critical review and meta-analysis. Br J Psychiatry. 2016;208(3):223–31. doi:10.1192/bjp.bp.114.156554. **A critical review of anxiety literature against Hill's criteria for disease causality**.
41. Tully PJ, Winefield HR, Baker RA, Denollet J, Pedersen SS, Wittert GA, et al. Depression, anxiety and major adverse cardiovascular and cerebrovascular events in patients following coronary artery bypass graft surgery: a five year longitudinal cohort study. Biopsychosoc Med. 2015;9:14. doi:10.1186/s13030-015-0041-5.
42. Frasure-Smith N, Lespérance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry. 2008;65(1):62–71. doi:10.1001/archgenpsychiatry.2007.4.
43. Martens EJ, de Jonge P, Na B, Cohen BE, Lett H, Whooley MA. Scared to death? Generalized anxiety disorder and cardiovascular events in patients with stable coronary heart disease: The Heart and Soul Study. Arch Gen Psychiatry. 2010;67(7):750–8. doi:10.1001/archgenpsychiatry.2010.74.
44. Tully PJ, Cosh SM, Baune BT. A review of the affects of worry and generalized anxiety disorder upon cardiovascular health and coronary heart disease. Psychol Health Med. 2013;18(6):627–44. doi:10.1080/13548506.2012.749355.
45. Roest AM, Zuidersma M, de Jonge P. Myocardial infarction and generalised anxiety disorder: 10-year follow-up. Br J Psychiatry. 2012;200(4):324–9. doi:10.1192/bjp.bp.111.103549.
46. Goodwin RD, Davidson KW, Keyes K. Mental disorders and cardiovascular disease among adults in the United States. J Psychosom Res. 2009;43(3):239–46.
47. Thayer JF, Friedman BH, Borkovec TD. Autonomic characteristics of generalized anxiety disorder and worry. Biol Psychiatry. 1996;39(4):255–66. doi:10.1016/0006-3223(95)00136-0.
48. Kawachi I, Sparrow D, Vokonas PS, Weiss ST. Decreased heart rate variability in men with phobic anxiety (data from the Normative Aging Study). Am J Cardiol. 1995;75(14):882–5.
49. Baune BT, Stuart M, Gilmour A, Wersching H, Heindel W, Arolt V, et al. The relationship between subtypes of depression and cardiovascular disease: a systematic review of biological models. Transl Psychiatry. 2012;2, e92. doi:10.1038/tp.2012.18.
50. Barger SD, Sydeman SJ. Does generalized anxiety disorder predict coronary heart disease risk factors independently of major depressive disorder? J Affect Disord. 2005;88(1):87–91.
51. Bankier B, Barajas J, Martinez-Rumayor A, Januzzi JL. Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. Eur Heart J. 2008;29(18):2212–7. doi:10.1093/eurheartj/ehn326.
52. Parker G, Hyett M, Hadzi-Pavlovic D, Brotchie H, Walsh W. GAD is good? Generalized anxiety disorder predicts a superior five-year outcome following an acute coronary syndrome. Psychiatry Res. 2011;188(3):383–9. doi:10.1016/j.psychres.2011.05.018.
53. Kidd T, Poole L, Leigh E, Ronaldson A, Jahangiri M, Steptoe A. Attachment anxiety predicts IL-6 and length of hospital stay in coronary artery bypass graft surgery (CABG) patients. J Psychosom Res. 2014;77(2):155–7. doi:10.1016/j.jpsychores.2014.06.002.
54.•• Chalmers J, Quintana DS, Abbott MJ-A, Kemp AH. Anxiety disorders are associated with reduced heart rate variability: a meta-analysis. Front Psych. 2014;5. doi:10.3389/fpsyt.2014.00080. **A meta-analysis showing anxiety disorders relationship with heart rate variability**.
55. Tully PJ, Newland RF, Baker RA. Cardiovascular risk profile before coronary artery bypass graft surgery in relation to depression and anxiety disorders: an age and sex propensity matched study. Aust Crit Care. 2015;28(1):24–30. doi:10.1016/j.aucc.2014.04.006.
56. Fleet R, Lavoie K, Beitman BD. Is panic disorder associated with coronary artery disease? A critical review of the literature. J Psychosom Res. 2000;48(4–5):347–56.
57. Katerndahl DA. The association between panic disorder and coronary artery disease among primary care patients presenting with chest pain: an updated literature review. J Clin Psychiatry. 2008;10(4):276–85.
58. Isensee B, Wittchen HU, Stein MB, Hofler M, Lieb R. Smoking increases the risk of panic: findings from a prospective community study. Arch Gen Psychiatry. 2003;60(7):692–700.
59. Hoertel N, Le Strat Y, De Maricourt P, Limosin F, Dubertret C. Are subjects in treatment trials of panic disorder representative of patients in routine clinical practice? Results from a national sample. J Affect Disord. 2013;146(3):383–9. doi:10.1016/j.jad.2012.09.023.
60. Muotri RW, Bernik MA. Panic disorder and exercise avoidance. Rev Bras Psiquiatr. 2014;36:68–75.
61. Fleet R, Foldes-Busque G, Grégoire J, Harel F, Laurin C, Burelle D, et al. A study of myocardial perfusion in patients with panic

disorder and low risk coronary artery disease after 35% CO2 challenge. J Psychosom Res. 2014;76(1):41–5.
62. Fleet R, Lesperance F, Arsenault A, Gregoire J, Lavoie K, Laurin C, et al. Myocardial perfusion study of panic attacks in patients with coronary artery disease. Am J Cardiol. 2005;96(8):1064–8. doi:10.1016/j.amjcard.2005.06.035.
63. Sullivan GM, Kent JM, Kleber M, Martinez JM, Yeragani VK, Gorman JM. Effects of hyperventilation on heart rate and QT variability in panic disorder pre- and post-treatment. Psychiatry Res. 2004;125(1):29–39.
64. Yeragani VK, Pohl R, Balon R, Jampala VC, Jayaraman A. Twenty-four-hour QT interval variability: increased QT variability during sleep in patients with panic disorder. Neuropsychobiology. 2002;46(1):1–6.
65. Pohl R, Yeragani VK. QT interval variability in panic disorder patients after isoproterenol infusions. Int J Neuropsychopharmacol. 2001;4(1):17–20.
66. Vural M, Satiroglu O, Akbas B, Goksel I, Karabay O. Coronary artery disease in association with depression or anxiety among patients undergoing angiography to investigate chest pain. Tex Heart Inst J. 2009;36(1):17–23.
67. Roy-Byrne PP, Schmidt P, Cannon RO, Diem H, Rubinow DR. Microvascular angina and panic disorder. Int J Psychiatry Med. 1989;19(4):315–25.
68. Cicek Y, Durakoglugil ME, Kocaman SA, Guveli H, Cetin M, Erdogan T, et al. Increased pulse wave velocity in patients with panic disorder: independent vascular influence of panic disorder on arterial stiffness. J Psychosom Res. 2012;73(2):145–8.
69. Katzman MA, Bleau P, Blier P, Chokka P, Kjernisted K, Van Ameringen M, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1:S1–S. doi:10.1186/1471-244X-14-S1-S1.
70. National Institute for Health and Clinical Excellence. Generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults: management in primary, secondary and community care. 2011.
71. Sowden GL, Huffman JC. The impact of mental illness on cardiac outcomes: a review for the cardiologist. Int J Cardiol. 2009;132(1):30–7. doi:10.1016/j.ijcard.2008.10.002.
72. Schwartz SM, Trask PC, Ketterer MW. Understanding chest pain: what every psychologist should know. J Clin Psychol Med Settings. 1999;6(4):333–51. doi:10.1023/A:1026215730296.
73.• Tully PJ, Sardinha A, Nardi AE. A new CBT model of Panic Attack Treatment in Comorbid Heart Diseases (PATCHD): how to calm an anxious heart and mind. Cogn Behav Pract. 2016. doi:10.1016/j.cbpra.2016.05.008. **Recent description of a new CBT treatment model for panic attack, panic disorder, or anxiety due to CHD or HF in adults, based on clinical efficacy data**.
74. Tully PJ, Turnbull DA, Horowitz JD, Beltrame JF, Selkow T, Baune BT, et al. Cardiovascular Health in Anxiety or Mood Problems Study (CHAMPS): study protocol for a randomized controlled trial. Trials. 2016;17:18. doi:10.1186/s13063-015-1109-z.
75. Blumenthal JA, Feger BJ, Smith PJ, Watkins LL, Jiang W, Davidson J, et al. Treatment of anxiety in patients with coronary heart disease: rationale and design of the UNderstanding the benefits of exercise and escitalopram in anxious patients with coronary heart disease (UNWIND) randomized clinical trial. Am Heart J. 2016;176:53–62. doi:10.1016/j.ahj.2016.03.003.
76. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with coronary artery disease. Coch Data Syst Rev. 2011; (9): CD008012. doi:10.1002/14651858.
77. Sheps DS, Freedland KE, Golden RN, McMahon RP. ENRICHD and SADHART: implications for future biobehavioral intervention efforts. Psychosom Med. 2003;65(1):1–2.
78. Tully PJ, Baumeister H. Collaborative care for comorbid depression and coronary heart disease: a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2015;5(12), e009128. doi:10.1136/bmjopen-2015-009128.
79. Rafanelli C, Sirri L, Grandi S, Fava GA. Is depression the wrong treatment target for improving outcome in coronary artery disease? Psychother Psychosom. 2013;82(5):285–91. doi:10.1159/000351586.