

Depression and cardiovascular comorbidity

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Depression has long had a popular link to cardiovascular disease and death. However, only during the last 15 years has scientific evidence supporting this common wisdom been available. Beginning in the early 1990s, there began to accumulate community-based epidemiological evidence that medically healthy, depressed patients followed for long periods of time were at increased risk of both cardiovascular disease and cardiac death. In the mid-1990s, evidence appeared to indicate that depression following a heart attack increased the risk of death. It is now apparent that depression aggravates the course of multiple cardiovascular conditions. There are two major unanswered questions. One is whether treating depression will reduce the risk of cardiovascular disease and death. Here, preliminary, but not definitive, evidence suggests that the serotonin reuptake inhibitors may be useful. The other unanswered question regards the mechanisms that underlie this link between depression and cardiovascular disease. There is strong evidence linking platelet activation, autonomic activity, and inflammatory markers to both depression and heart disease, but why these links exist is far less clear.

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When psychiatrists use the term “comorbidity” in connection with depression, they are almost always referring to other psychiatric conditions, primarily anxiety or addictive disorders, and these do co-occur with depression more often than would be expected by chance.¹ However, vascular disease, particularly the association between depression and heart disease, is among the best-documented of all comorbidities.² Not only writers and poets, but our language itself refers to, “dying of a broken heart.” Almost all languages, in one way or another, express a very similar idea. However, in spite of this widespread popular acceptance, scientific evidence has been slow in emerging, and has turned out to be of a more complicated nature than expected.

Cardiovascular disease in depressed patients

Early epidemiological studies relating melancholia to heart disease found much higher rates of cardiovascular deaths in melancholic patients, but their use of hospitalized populations confounded the effects of depression and chronic institutionalization.³ After the Second World War, more psychoanalytic formulations, primarily “type A personality,” held sway. The time-urgent, angry, type A individual did seem significantly more vulnerable to heart disease,

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Selected abbreviations and acronyms

ENRICH *Enhancing Recovery in Coronary Heart Disease*

MDD *major depressive disorder*

MI *myocardial infarct*

SADHART *Sertraline Antidepressant Heart Attack Randomized Trial*

SSRI *selective serotonin reuptake inhibitor*

but by the mid-1970s the association became increasingly difficult to replicate. Although we will never know for certain, in retrospect it seems likely that the adverse consequences of the type A personality were real, but were mediated by the sympathetic nervous system.⁴ As cardiologists began to routinely use β -blockers after myocardial infarct (MI), the significance of the type A personality dissipated. In the mid-1970s, interest returned to the concept of major depression and cardiac disease or cardiac death. A Danish epidemiologist was the first to show that patients coming to treatment with a diagnosis of major depressive disorder (MDD) or manic-depressive disease were more likely to die from cardiac causes than the rest of the Danish population.⁵ Dozens of replications have been reported, but it quickly became clear that these clinical populations confounded diagnosis and treatment. Using community, rather than clinical, samples circumvented the problem of treatment effect, because in community samples few cases were in treatment. The concern was that community cases as opposed to clinical cases of MDD would be considerably milder in severity, thereby masking the relationship. However, when the first community surveys appeared in the late 1980s the relationship between major depression and cardiac death persisted.⁶ At the same time that these first community surveys began to appear, other studies were drawing attention to the relationship between MDD and cigarette-smoking.^{7,8} Depressed patients were more likely to smoke and less likely to be able to stop, and yet up to that time epidemiologists had never controlled for smoking while examining the relationship between depression and heart disease.⁹ It could merely be that depressed patients were more likely to smoke, and that smoking caused heart disease. Anda, a cardiovascular epidemiologist with the Communicable Disease Center in the US Public Health Service, was the first to control for smoking, as well as multiple other cardiac risk factors that might influence the relationship with depression.¹⁰ Using a hopelessness scale rather than a diagnosis of MDD, the

relationship again persisted. The more depressed the individual, the more likely that individual was to suffer a MI and to die from cardiac causes. In 2002, less than 10 years after Anda's original study, Wulsin at the National Heart, Lung, and Blood Institute published a meta-analysis that found ten large studies that now controlled for cardiovascular risk factors, including smoking.² All ten found coronary heart disease to be more common in depressed patients, and the increase was statistically significant in seven of the ten studies. The risk existed not only in major depression, but also in minor depression, and it existed in both males and females (*Figure 1*).

The evidence that has been presented up until now is primarily from epidemiological studies that started with essentially medically healthy, depressed young adults and followed them for long periods of time. Beginning with medically healthy individuals avoided the potential criticism that the association of depression with heart disease was merely the result of the patient's depressive reaction to the symptoms of heart disease. However, such studies required either very large samples or decades of follow-up. In the late 1980s, Carney suggested that depression might have an adverse impact on the course of coronary artery disease in depressed patients who already have heart disease.¹¹ Using this approach, Nancy Frasure-Smith and Françoise Lesperance were able to show that post-MI patients with a diagnosis of MDD were more than three and a half times more likely to die

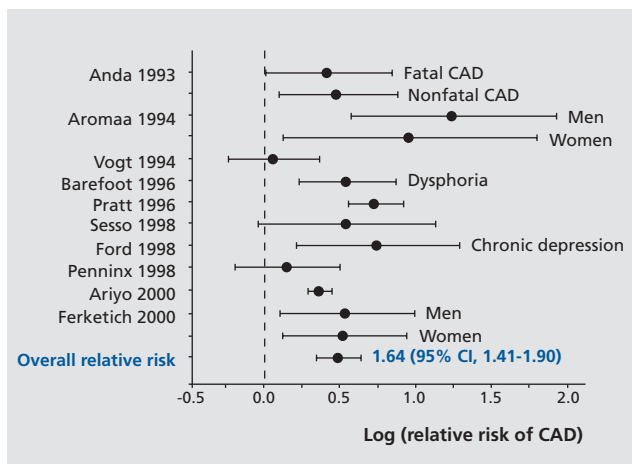


Figure 1. Relative risk of coronary artery disease (CAD) in depressed patients; a meta-analysis of 10 studies.

Adapted from ref 2: Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. *Psychosom Med.* 2003;65:201-210. Copyright © Lippincott, Williams & Wilkins 2003.

than post-MI patients without MDD.¹² In their 1993 study, they performed a structured psychiatric examination in 222 consecutive post-MI cases at the Montreal Heart Hospital and followed them for 6 months. Using similar approaches, multiple investigators have now looked at this effect of depression on the course of coronary artery disease following an MI. In 2005, Evidence Reports/Technology Assessment of the Agency for Health Care Research and Quality (AHRQ), a branch of the US department of Health and Human Services, found 17 post-MI studies that assessed the relationship between depression and subsequent mortality.¹³ These studies ranged from 4 months to as long as 10 years after a coronary event, and concluded that the evidence was strikingly consistent, and that post-MI depression is associated with about a threefold increase in cardiac mortality.² The review included studies that looked at the influence of both major and less than major depression. Several studies performed on large post-MI samples have now looked at the effect of increasing severity of depressive symptoms, and there is a consistent positive association between the severity of depressive symptoms and an increased risk of mortality.^{14,15} Even since the 2005 Evidence Reports/Technology Assessment¹³ review was published 2 years ago, additional evidence has continued to accumulate.^{16,17} In addition to the increased risk of acute coronary syndromes, depression has also been associated with increased mortality in congestive heart failure¹⁸ and following ischemic stroke (Figure 2).^{19,20}

Reducing mortality from cardiovascular disease by treating depression

The obvious question raised by the strong association between depression and cardiac mortality is whether treatment of depression would reduce mortality. Enhancing Recovery in Coronary Heart Disease (ENRICHD)²¹ was a randomized, controlled trial sponsored by the National Heart, Lung, and Blood Institute (NHLBI). This trial tested whether cognitive behavioral therapy (CBT) reduced mortality in patients after MI compared with usual care. CBT reduced depression modestly but did not alter mortality. The original ENRICHD article²¹ reported briefly that 20% of the 1853 depressed patients received antidepressant drugs, and that those individuals had a statistically significant (42%) reduction in a combined end point of death or recurrent MI, but this observation came from data that was neither ran-

domized nor controlled. Several years later, Taylor published a much more detailed analysis of antidepressant drug use in the ENRICHD trial.²² Among many other problems, the absence of randomization was not subtle; only those known to be at higher risk for cardiac events were offered antidepressants. In addition, there was no control over when the drug was started or stopped. Nevertheless, the sample was very large, the number of events reasonable, and the magnitude of the effect is hard to ignore (hazard ratio, 0.57 [95% confidence interval, 0.38-0.84]). This is a post-hoc observation, not an a priori test of a hypothesis. However, it is a strong signal that antidepressant drugs can reduce life-threatening events. Another hint that antidepressants can reduce post-MI mortality came from the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART). Patients admitted with either acute MI or unstable angina were screened for MDD and, if suitable, randomized to sertraline or a placebo to test the drug's safety and efficacy.²³ This was done as a stepping-stone towards testing whether a selective serotonin reuptake inhibitor (SSRI) could reduce mortality. SADHART did demonstrate the safety and efficacy of sertraline. It also, rather unexpectedly, showed a reduced risk of death and recurrent MI similar to that seen in the ENRICHD trial. However, with only 369 patients, SADHART had almost 10-fold fewer patients than a power analysis suggested would be needed to adequately evaluate the effect of sertraline on mortality. Although the study was randomized and controlled, the results, as would be expected, did not reach statistical significance.

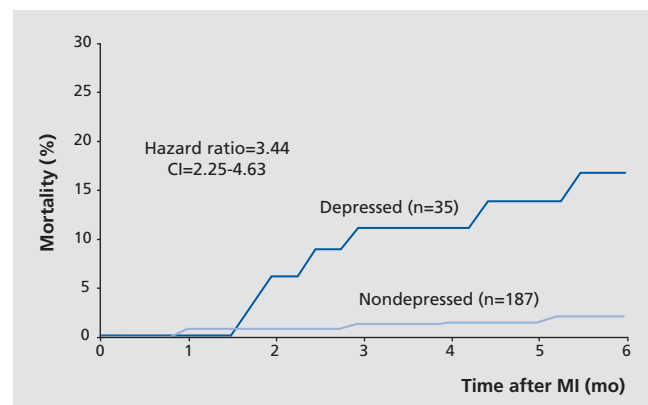


Figure 2. Cumulative mortality in depressed and nondepressed patients following myocardial infarct (MI). Adapted from ref 12: Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA*. 1993 20;270:1819-1825. Copyright © American Medical Association 1993

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A 2003 Danish poststroke study also showed a strong trend for reduction of life-threatening events by SSRIs.²⁴ Although SSRI treatment was randomized and controlled, observations of reduced morbidity and mortality were made post hoc and were not evaluated blindly. None of these studies constitutes an adequate scientific test of the question. SADHART and ENRICHD both examined depressed, postcoronary patients and found evidence that SSRIs might reduce medical morbidity. Interestingly, the stroke trial was not conducted in depressed patients, but rather was a depression prevention trial. The three trials taken together offer strong evidence that SSRIs may reduce post-MI medical morbidity and mortality, but a definitive clinical trial is needed. The Danish stroke study is interesting, because the SSRI was given exclusively to nondepressed patients. This raises the issue of whether the benefit of SSRIs in patients with vascular disease may extend beyond depressed patients. There is a single, recent poststroke study with a similar design that failed to find either a significant ability of an SSRI to prevent depression or to reduce subsequent medical events.²⁵

The suggestion that SSRIs may have a beneficial effect on cardiovascular outcomes comes not only from randomized trial data, but from epidemiological studies as well. Initially, Cohen examined the hospital and pharmacy records of 55 000 New York City health and hospital workers, and found those taking a tricyclic antidepressant (TCA) were twice as likely to be hospitalized with a diagnosis of MI than those not prescribed an antidepressant drug.²⁶ In contrast, individuals prescribed an SSRI were no more likely to have an MI. This observation of a beneficial effect of SSRIs has been replicated in four of the five epidemiological studies that are available to address this issue.²⁷⁻³¹ However, unlike SADHART and ENRICHD, these are epidemiological studies, not clinical trials. Although suggestive, epidemiological data can not establish a cause-and-effect relationship. These studies primarily examine the rate of new MI in individuals who are assumed to be depressed because they are taking antidepressants, compared with the rate in individuals who are free of antidepressants and assumed not to be depressed. If SSRIs do reduce the risk of MI as the data suggests, this raises an interesting issue. SSRIs but not TCAs are known to reduce the “stickiness” of platelets. This effect, although involving mechanisms somewhat distinct from those of aspirin, could result in a reduction in the risk of MI similar to that provided by

aspirin.^{32,33} This does not, however, imply that the same mechanism involved in the prevention of MI in patients with no prior history of cardiac disease would be responsible for the reduction in mortality in patients given an SSRI following an MI, as suggested by the data from SADHART and ENRICHD. These post-MI patients, unlike the depressed patients with no known prior history of cardiac disease, will already be receiving multiple antiplatelet drugs, and it is unlikely that the addition of another antiplatelet compound would have a dramatic impact on mortality.

Another interesting observation from Cohen’s study in hospital workers is related to the risk of developing heart disease among patients suffering depression.²⁶ He observed that the 1653 workers who filled prescriptions for TCAs (and were presumably depressed) were more than 100% more likely to have an MI than those 55 000 individuals who were not taking TCAs. This compares with the Wulsin ten-study meta-analysis² where depressed individuals had essentially a 65% increase in the risk of developing coronary disease. Although the studies are not absolutely comparable, the major difference is that all of the studies in the Wulsin analysis controlled for smoking as well as other cardiac risk factors, while Cohen had no data on, and could not control for, such risk factors. Both studies were based on large samples and, although this is not an ideal way to approach the issue, they illustrate two different points of view. The epidemiologist asks whether depression makes an independent contribution to the risk of heart disease, or if it is only an apparent increase accounted for by the fact that depressed patients are more likely to smoke, and smoking causes heart disease. Wulsin’s data says that there is a 65% increase beyond that accounted for by any known risk factors. The clinician faced with a depressed patient may ask how much more likely this person is to develop coronary artery disease than a similar person without depression. For the specific patient, there exists both the independent risk associated with depression plus those cardiac risk factors known to be associated with depression such as smoking, poor health behaviors, obesity, diabetes, reduced physical activity, etc. Thus, while Wulsin’s estimate of a 65% increase in risk may be scientifically more accurate, Cohen’s estimate of more than a 100% increase is likely to be a clinically more relevant assessment of the problem.

Up to this point, what has been discussed is the evidence that medically healthy, depressed patients are more likely

to develop and die of heart disease than those without depression, and that depressed patients who already have heart disease, particularly acute coronary syndromes (ACS—this refers to both MI and unstable angina) are at a markedly increased risk of cardiac death. In addition, evidence has been reviewed suggesting that SSRI treatment may possibly reduce this medical morbidity and mortality. What has not been discussed is what drives these associations. It is important to make a number of distinctions. There are undoubtedly multiple pathways connecting depression and heart disease, and although some pathways may operate in both medically healthy depressed patients and in those with pre-existing cardiac disease, some could be unique to one situation or the other. In addition, the mechanisms that lie behind the reduction in risk with SSRIs (if that reduction is confirmed), may also not be exactly the same as the mechanism that created the risk.

Multiple mechanisms linking depression and heart disease have been suggested. Depression has regularly been demonstrated to lower adherence to prescribed medication and secondary prevention measures^{34,35} among cardiac patients. Studies of noradrenergic activity,³⁶ autonomic activity,^{37,38} heart rate variability (HRV),^{39,40} and platelet biomarkers,⁴¹⁻⁴³ as well as inflammatory markers,⁴³⁻⁴⁶ have regularly found differences in clinically depressed compared with nondepressed post-MI patients that favor the development of heart disease. Levels of omega-3 fatty acids are known to vary between depressed and nondepressed populations and influence the risk of ischemic heart disease.⁴⁷ The possibility also exists that depression and vascular disease share certain vulnerability genes.⁴⁸ However, why depression and heart disease are so closely associated is far from clear. A detailed discussion of each of these potential mechanisms is beyond the scope of this review, but recent references are supplied.^{49,50}

Although not as immediately obvious as the question of potential mechanisms, a very important issue is that of when these mechanisms come into play. The relationship between depression and heart disease that has been documented is an association. Associations do not explain causality, and can result from multiple different pathways. Certainly some of the depressive symptomatology and even some of the major depression that arises for the first time following a coronary event is a reaction to that medical event. However, there is considerable evidence that such cases are not an explanation for most of the associ-

ation between depression and heart disease. Two different pieces of information are pertinent. Earlier in this review it was mentioned that the 1993 study by Anda was the first epidemiological study to control for cardiac risk factors. It was also the first study to carefully control for prior medical illness.¹⁰ It was based on a follow-up of the National Health and Human Nutrition Examination Survey (NHANES) and involved over 3000 individuals collected at that time for more than 13 years. At baseline, individuals in this study had both a physical exam and laboratory tests, and anyone with known medical illness was excluded. In addition, to be certain that any depression found at baseline was not the result of subtle symptomatology that distressed the individual but was not recognized or reported, the first 2½ years of data were excluded from the analysis. As a result, the cardiac disease and deaths that occurred over the last 11 years could unequivocally be attributed to pre-existing depression. When Wulsin published his meta-analysis 10 years later, all 10 studies that were included controlled in one way or another for baseline medical illness.

The other evidence indicating that pre-existing heart disease is not the major cause of the association between depression and heart disease comes from the SAD-HART study. When we initially planned that study, our expectation was that many of the cases of major depression that are observed in the intensive care or step-down units after hospitalization for MI would be mild and of very short duration. That was our expectation, because we felt that an MI causes both severe psychological and physiological stress, and it would not be surprising that in vulnerable people, it could produce depression.⁵¹ Our expectation that many cases of post-MI depression would be mild was confirmed, but the idea that they would for the most part begin in the hospital after the coronary event and be of short duration was not correct. Fifty-three percent of the cases began before hospitalization. Coronary events, either MI or unstable angina, are acute events. Ninety percent of patients hospitalized for MI are hospitalized within the first 24 hours. Ninety-three percent of the depressions that began before hospitalization began more than a month before hospitalization, and that is probably an underestimate of how many depressions actually began before the coronary event. SAD-HART was a clinical trial that randomized patients to sertraline or placebo, not an epidemiological study. It would not be considered ethical to recruit post-MI patients who were already being treated with antide-

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pressant drugs into the trial. This would mean taking someone who was on antidepressant medication, stopping their medication, and randomizing them potentially to a placebo. About 20% of patients who met the criteria for major depression were already receiving an antidepressant drug. As a result, probably closer to 70% of the patients observed to be depressed following their MI in the SADHART study actually had that depression prior to the coronary event. For these patients, the depression may have contributed to the coronary event, but the coronary event did not precipitate the depression. There was a similar incidence of MDD cases beginning before hospitalization in the ENRICH trial (Carney, personal communication).

Is cardiovascular disease a cause of depression?

The fact that most coronary disease follows rather than precedes depression does not imply that depression causes coronary artery disease. It could be that some of the biological changes associated with depression do increase the risk of coronary or vascular disease. However, it is also perfectly plausible that preceding genetic or environmental events could lead to biological changes conducive to both conditions. When thinking about the relationship between depression and heart disease, it is easy to make the mistake of looking for a single cause.

For a period of time, it was popular to consider the platelet abnormalities associated with depression as the cause of the association between depression and heart disease. However, it is extremely unlikely that there will turn out to be any single cause. Platelets, health behaviors, inflammatory markers, autonomic abnormalities, etc, will each undoubtedly turn out to play a role. Not only will there be multiple mechanisms; in any given patient the degree to which a given mechanism creates the association will vary. In addition, the mechanisms underlying the association between depression and heart disease may not be exactly the same as the mechanisms underlying the ability of SSRI drugs to alter that association. Once an individual develops depression, especially if it is recurrent, that illness brings with it a number of health behaviors that will unquestionably increase the risk for vascular disease. It has repeatedly been shown that depressed individuals are less likely to take care of their health, they are less likely to exercise, and are more likely

to be obese and find it difficult to stop smoking. In addition to issues directly connected to being depressed, there are some issues that precede depression; this may increase the risk for both depression and ischemic heart disease. A number of epidemiological studies have looked at early adverse experiences and their impact on multiple subsequent behaviors.^{52,53} There is a strong association between early abuse and neglect and subsequent depression, drug abuse, and ischemic heart disease. There is some evidence to suggest that childhood maltreatment, including both abuse and neglect, influences depression and heart disease in ways that are gender-dependent.⁵⁴ Evidence from the National Comorbidity Study indicates that although males are usually at higher risk for ischemic heart disease and females at higher risk for depression, early childhood maltreatment increases the risk of depression in males, while in females maltreatment raises the risk of ischemic heart disease in women so that it resembles that usually seen only in men.

In addition to childhood adverse events influencing both the risk for heart disease and depression, another mechanism by which both heart disease and depression could have common roots without either condition directly causing the other is shared genes. Data from the Vietnam Era Twin Registry in 2731 twin pairs showed a shared genetic risk between depression, hypertension, and heart disease.⁵⁵ Recently, there has been considerable evidence that functional variants in the serotonin transporter can alter the relationship between stress and subsequent depressive episodes. Individuals with two short alleles at the serotonin transporter locus were more sensitive to stressful events than individuals with either one or two long alleles.⁵⁶ Whether these same functional variants in a serotonin transporter can influence the risk of ischemic heart disease is at present unknown.

Discussion

There is strong evidence that depression is associated with an increased risk of cardiovascular disease and cardiac death. In studies of large populations free of medical disease, after controlling for all known cardiovascular risk factors, it is those individuals with baseline depression that are more likely to develop cardiovascular disease. And, once they develop coronary artery disease, those who are observed to be depressed are at markedly increased risk of cardiac morbidity and mortality. Interestingly, this increased risk is not limited to patients with major depres-

sion. Patients with less than major depression, who have even modest increases in symptoms of depression, show a higher risk of recurrent infarction and cardiac death.^{14,15} The more severe the depression, the higher the risk. Depression also increases the risk of death and medical complications after coronary bypass surgery⁵⁷ and in patients with heart failure as well.¹⁸ Similar to the risk of cardiovascular disease, individuals with depression are also at higher risk of ischemic stroke, and after a stroke, patients who are depressed are at higher risk of medical complications and death.^{19,20,58} There is even evidence that antidepressant treatment reduces these medical risks.⁵⁹ Most cases of major depression have their onset in the early adult years, and many become recurrent. This review has focused on these early-onset cases because they are the most common, and because examining such cases avoids confusing whether depression precedes vascular disease or whether the early symptoms of vascular disease are responsible for the onset of depression. There is no question that depression can precede vascular disease by decades. To what degree this early-onset depression itself leads to vascular disease, and to what extent the association is the result of a common antecedent, remains to be clarified. In addition to depression earlier in life, some cases of major depression clearly have their initial onset later in life, and a number of investigators have suggested that at least some of these cases are secondary to vascular changes in the brain. The earliest suggestions of such a relationship came from

poststroke studies⁶⁰ and more recently from imaging studies. Imaging studies have indicated that late-onset depression is more likely to show evidence of so-called white matter hyperintensities which are associated with hypertension and often thought to be evidence for arterial sclerotic changes in the brain.^{61,62} These issues are complex and are not dealt with in this review.

Nevertheless, it is worthwhile to realize that the relationship between depression and heart disease can be a two-way street. Most depressions seen after MI do have their onset long before the coronary episode. However, a significant number of individuals will develop their first depression after a coronary event. A high percentage of such depressions recover spontaneously, but a third of such individuals respond poorly to usual treatments, even though it is their first depression and is often mild. It is intriguing to consider whether depression in these cases has a vascular or aging component.

There remain two major unsettled questions. The first is whether treating depression reduces the risk of vascular disease. Although there is some suggestion that this is the case, the evidence available is not adequate, and a definitive trial is required. The second is why there is such a strong association between depression and vascular disease. Here, the available evidence is even more limited. Depression and cardiovascular disease are the two largest public health problems in the Western world, and their appropriate prevention and treatment is an enormous public health issue. □

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Depresión y comorbilidad cardiovascular

Popularmente la depresión se ha relacionado hace largo tiempo con la enfermedad cardiovascular y la muerte. Sin embargo, sólo durante los últimos quince años se ha contado con evidencia científica que respalde este conocimiento popular. Al inicio de la década de los noventa se comenzó a acumular evidencia epidemiológica de estudios en la comunidad de pacientes depresivos, médicamente sanos, que fueron seguidos por largos períodos de tiempo en quienes se encontró un mayor riesgo tanto de enfermedad cardiovascular como de muertes por causa cardíaca. A mediados de los noventa, la evidencia pareció indicar que la depresión post ataque cardíaco aumentaba el riesgo de muerte. Hoy está claro que la depresión agrava el curso de diversas patologías cardiovasculares. Hay dos preguntas principales sin responder. Una es si acaso el tratar la depresión reducirá el riesgo de enfermedad cardiovascular y de muerte. Para esta pregunta la evidencia sugiere, preliminar pero no definitivamente, que los inhibidores de la recaptación de serotonina pueden ser útiles. La otra pregunta sin responder se refiere a los mecanismos que subyacen a la relación entre depresión y enfermedad vascular. Existe una poderosa evidencia que relaciona la activación plaquetaria, la actividad autonómica y los marcadores de la inflamación tanto con la depresión como con la enfermedad cardíaca, pero el porqué existen estas relaciones aun no se ha aclarado.

Dépression et comorbidité cardiovasculaire

L'idée qu'il existe un lien entre dépression, maladie cardiovasculaire et décès est ancienne et populaire. Il a fallu néanmoins attendre ces 15 dernières années pour disposer d'arguments scientifiques confirmant ce bon sens commun. Au début des années 90, des preuves épidémiologiques basées sur la population générale ont commencé à s'accumuler en faveur de l'augmentation du risque conjoint de maladie cardiovasculaire et de décès cardiaque chez des patients déprimés, médicalement sains et suivis sur de longues périodes. Au milieu des années 90, il a été montré que la dépression après une crise cardiaque augmentait le risque de décès. Nous savons maintenant que la dépression aggrave l'évolution de nombreuses maladies cardiovasculaires. Deux questions majeures restent sans réponse : traiter la dépression réduira-t-il le risque de maladie cardiovasculaire et de décès ? Les inhibiteurs de la recapture de la sérotonine semblent répondre positivement au premier abord, mais pas de façon définitive. L'autre question concerne les mécanismes qui sous-tendent ce lien entre dépression et maladie cardiovasculaire. Activation plaquettaire, activité autonome et marqueurs inflammatoires sont très certainement liés à la dépression et à la maladie cardiovasculaire mais pourquoi le sont-ils ? Voilà qui est loin d'être compris.

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