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Depression and Poor Adherence t Lipid-Lowering Medications Among Patients with Coronary Artery Disease

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In an article published in the *Journal of the American Medical Association* in 1975, the Coronary Drug Project investigators reported that "there is no evidence of significant efficacy of clofibrate with regard to total mortality or cause-specific mortality."[1] The study showed that patients treated with the lipid-lowering drug clofibrate had a 20.0% mortality rate at 5 years compared to a 20.9% rate in those given placebo. Five years later in the *New England Journal of Medicine*, evidence from the same study showed that patients who were "good adherers" to clofibrate (that is, those who took 80% or more of their prescribed pills) had a significantly lower mortality (15.0%) than did those who were "poor adherers" to clofibrate (24.6%).[2] This observation seemed to provide evidence that clofibrate was valuable in the treatment of heart disease. However, it was only part of the story. Similar findings were noted in those assigned to placebo; those who were "good adherers" to an inactive tablet had a much lower mortality (15.1%) than those who were "poor adherers" (28.3%).

In this issue of the *Journal of Psychosomatic Research*, May, et al.[3] report that patients with coronary artery disease (CAD) in the Intermountain Healthcare system who also had an ICD-9 diagnosis of depression were less likely to adhere to lipid-lowering treatment than those without an ICD-9 diagnosis of depression. This study adds to a growing body of literature demonstrating a strong association between depression and poor adherence. It has previously been reported that the odds are three times greater that depressed patients will not adhere to medical treatment recommendations than those without depression.[4]

The relationship of depression and poor adherence to lipid-lowering therapy reported by May, et al.[3] is potentially of great importance. Adherence to statins is associated with lower mortality,[5,6] although the explanation for this relationship is not as straightforward as it might first appear. It seems self-evident that in order to benefit from the well-recognized biological effects of statins, a patient must take them. Those who adhere to statins will improve and those who do not adhere won't. This is almost certainly not the entire story, however. In one study,[5] good adherence to statins was associated with an approximate 50%

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reduction in all-cause mortality, an observation that cannot be explained by drug effect alone. It has been noted that to achieve a mortality reduction of this magnitude, taking statins as prescribed would have to prevent 100% of all cardiovascular deaths as well as a significant proportion of deaths from other causes.[7] Another possible explanation is the so-called "healthy adherer" effect,[7] a term used to describe the observation that individuals who adhere to the advice of health care providers are healthier than individuals who do not. This is said to explain why good adherers in so many cardiovascular disease trials had an almost identically lower mortality than poor adherers regardless of whether they were assigned active treatment or placebo.[2,8-10] Good adherers to statins may also have lower mortality than poor adherers because so-called "poor adherers" may stop taking these medications because of competing comorbidities that themselves may be fatal (e.g., cancer). It is also possible that poor adherence is associated with other conditions that increase mortality. More than a decade ago, McDermott, et al. demonstrated that good adherence is associated with reduced morbidity and mortality among patients with, or at risk for, CAD and congestive heart failure.[11] The authors concluded that "adherence is a marker of some unidentified health care behavior that is itself linked to prognosis." At the time, our group suggested the possibility that non-adherence is a marker of depression, and that depression, in turn, is independently associated with increased mortality in those with heart disease.[12] The findings of May, et al.[3] bring this possibility to the forefront of the discussion yet again.

We must be somewhat cautious in interpreting the results of this study, however, since neither depression nor adherence to medical therapy was directly measured in this report. It must also be noted that not all patients prescribed a lipid-lowering medication necessarily had the same need for one. The prescription of a lipid-lowering medication was part of a standardized discharge medication protocol used in the Intermountain system for all patients diagnosed with CAD.[3] The use of standardized discharge medication protocols of this type makes it less likely that patients who should receive lipid-lowering treatment are discharged without it. In one study, use of a standard discharge medication protocol for patients with CAD increased the utilization of lipid-lowering medications at the time of discharge from 6% (before protocol implementation) to 86% and from 10% to 91% at 1 year.[13] However, there are some patients with CAD whose lipids are at, or below, established goals even without treatment. If a patient received a prescription for lipid-lowering therapy, but took it sporadically because he or she was at goal without it, that patient would have been considered to be non-adherent in this study. This would also be true for those patients who split their pills or who used alternate-day dosing, a practice sometimes done as a cost-saving measure or to limit side effects, often in collaboration with health care providers. Since different tablet strengths for many medications are often quite similar in cost, tablet splitting[14] or alternate-day dosing[15] can lower the cost of medications considerably. If a provider prescribed a 30-day supply of a lipid-lowering medication to a patient in this study at a tablet strength twice that of what the patient actually needed, knowing that the patient would either split the tablet or take it every other day, the patient might be considered non-adherent if the patient then refilled the medication after 60 days. Thus, "non-adherence" by patients in this study might have been deliberate, and even appropriate. Adjusting medication dosing because of cost or perceived side effects might be expected to be more common among those with depression, given the relationship between depression and lower socioeconomic status[16] and greater concerns about medication side effects.[17] It is also not clear how many people with an ICD-9 diagnosis of depression in this report actually were depressed, since there was no assessment of depression made as part of the study protocol. It has been shown that there is only fair-to-moderate agreement between administrative definitions and self-report of depression.[18]

The relationship among adherence, depression, and mortality has important public health implications. The more thoroughly we define this relationship, the better able we will

determine whether strategies to enable depressed, non-adherent patients to reap the benefit of effective medications for heart disease should target depression, adherence, or both. The issue of how to improve adherence in depressed patients with heart disease was addressed more than a decade ago, when the American Heart Association convened an expert panel on the topic of adherence[19] and the question was asked, “Would antidepressant treatment make a difference to compliance—and mortality?” [20] Although the answer to this question is still uncertain, there is now evidence that among those with heart disease, when depression improves, so too does adherence. Rieckmann, et al.[21] showed that patients surviving an acute coronary syndrome who had the most severe depressive symptoms demonstrated the poorest adherence to aspirin during follow-up. However, those patients whose depression improved in the first month after the acute event demonstrated improvements in adherence rates in the subsequent two months. In another study,[22] medication adherence among depressed patients with an acute coronary syndrome improved in those who experienced complete remission of depression. These findings parallel the observations on adherence to antiretroviral treatment among depressed patients with HIV infection.[23-27]

In summary, the findings of May, et al.[3] highlight the important relationship between depression and adherence among patients with CAD. There are many factors that affect adherence to medical treatment regimens, and depression is without question an important, and potentially modifiable, one. To improve adherence, medical regimens have to be kept simple, drugs should be affordable, medications with particularly bothersome side effects need to be avoided, and health insurance coverage must be improved. However, simpler, more affordable, and better tolerated medications are not likely to solve adherence problems in depressed patients unless their depression is successfully treated.

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