Poor Compliance: The Hidden Risk Factor

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In recent years it has become abundantly clear that medical regimens designed to lower risk factors for coronary heart disease, including hypertension and hyperlipidemia, can have profound effects on coronary morbidity and mortality. Meta-analyses of low-density lipoprotein (LDL) cholesterol–lowering trials using statins, for example, have demonstrated that morbidity and mortality can be reduced by about one third, an effect that can be demonstrated equally in men and women and in older and younger subjects [1]. However, cholesterol-lowering regimens, as well as other risk factor interventions, can only be successful if patients, in fact, follow them. It has been said that “cardiovascular events are coming to be regarded as a medical failure rather than the first indication of treatment" [2]. That is probably true, but we can only realize the potential of these interventions if we are able to maximize patient compliance with them.

The dictionary defines compliance as "the act of conforming, acquiescing, or yielding" and defines adherence as "steady devotion, support, allegiance, or attachment" [3]. Neither of these definitions quite fits the behavior that we are seeking in prescribing medical regimens, which might be defined as maximizing the patient's conformance to an indicated medical regimen. Although there may be subtle differences, throughout this discussion I will refer to compliance and adherence interchangeably and use the term “compliance” whenever possible.

Compliance can be measured in several ways. The most common, of course, is the self-report from the patient; slightly more laborious are periodic pill counts; more sophisticated are the automated methods that use bar codes, containers that automatically count openings, and other more sophisticated methods for confirming or substituting for patient self-reports. Measurement of biologic markers thought to reflect regular drug taking is also useful, although such markers are subject to the "toothbrush" effect, (*ie*, strict compliance only preceding the time of planned measurement). Finally, direct measures of drug metabolites may be undertaken, although these too suffer from the fact that they may only reflect recent behavior [4].

There is little doubt that compliance remains a problem for the treatment of chronic disease. This is particularly true for compliance with cholesterol-lowering regimens used in the prevention of coronary heart disease. In a recent study of such regimens, antiplatelet, anticoagulant, and lipid-lowering therapy were compared in terms of their frequency of prescription [5]. Although none were prescribed in all patients in whom they were indicated, the frequency of lipid-lowering prescriptions was far lower than the others were (Fig. 1). The same phenomenon has been demonstrated in studies of the behavior of cholesterol lowering in patients with coronary heart disease in six European countries. Interestingly, there was considerable variation with the most aggressive treatment in Spain and Italy and the least aggressive in Sweden and the United Kingdom (the opposite of the coronary heart disease frequency rankings) [6]. Even when drugs for cholesterol lowering are prescribed, up to two thirds of patients may stop them within a year [7]. The reasons for this are not entirely clear. Some insight may be gained by the responses of patients in the 4S study [8] who, after the termination of the study, stopped the medication. A few stopped because of adverse effects or because they did not want to take the drug for other reasons, but the great majority either stopped because the cost was prohibitive or because their cholesterol was now normal—a state of affairs, of course, not likely to continue once they discontinue the medication [8].

Clinical trials, because they involve such intense follow-up, are not adequate reflectors of the potential for nonadherence. Among patients in trials taking bile acid sequestrants (*eg*, niacin, lovastatin, or gemfibrozil), the percentage of those discontinuing after 1 year was in every case considerably lower in the patients in trials than in those in health maintenance organizations [9].

It may seem intuitive that better adherence will be associated with better outcomes in terms of the variable intervened on, as well as better effects on morbidity and mortality. Indeed, in post-trial follow-up in patients in the 4S study, those who continued the medication had significantly lower serum cholesterol levels than those who did not [8]. On the other hand, in a review of outcomes in studies linking drug compliance to morbidity and mortality to compliance in patients at risk of congestive heart fail-

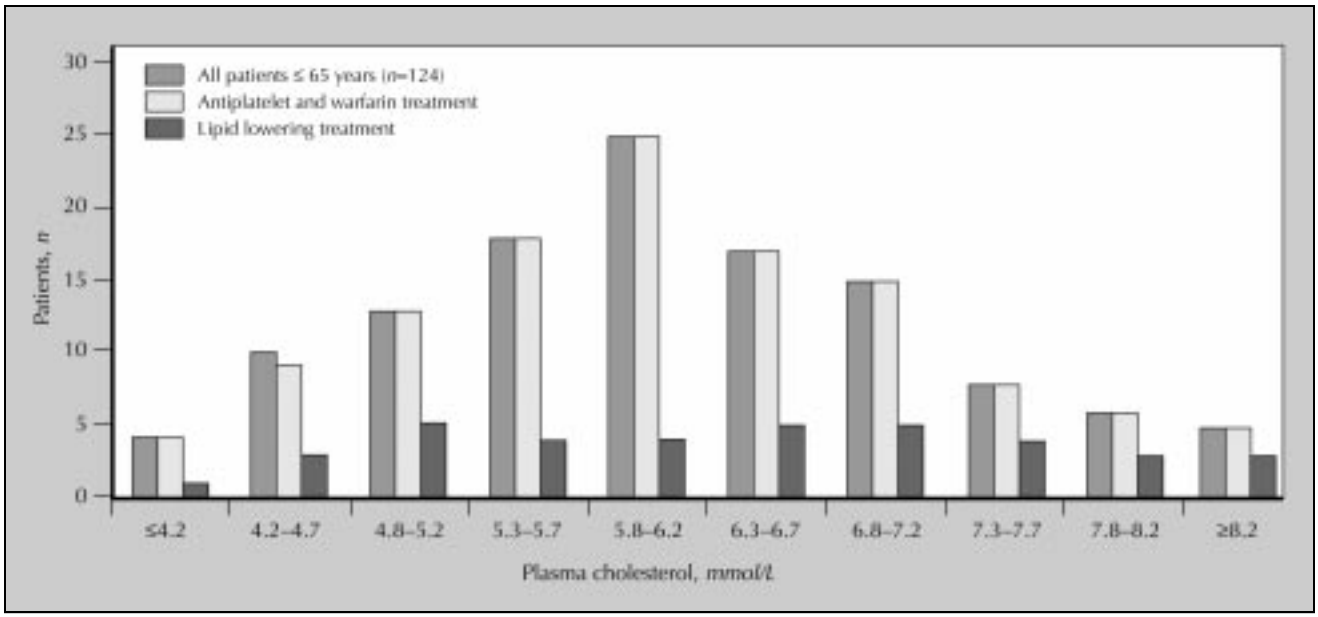

Figure 1. Patients receiving antiplatelet, anticoagulant, and lipid-lowering therapy, post-coronary artery bypass graft by cholesterol level. (*Adapted from* Delacretaz *et al*. [5].)

ure, results were not consistently in favor of better outcomes in patients with better adherence [10].

What are the factors that influence adherence? These may be divided into those associated with the disease itself, those emanating from patient behavior, those emanating from the treatment regimen, and those that reflect physician behavior.

It should come as no surprise that adherence is generally worse if the condition being treated is currently asymptomatic or only mildly symptomatic. Adherence is also worse with chronic conditions that require repeated daily behavior over an extended period of time and if there is a long lag time between noncompliance and its consequence [11]. In many patients with hypercholesterolemia, (or for that matter patients with hypertension or who smoke) all of these would apply.

Patient variables are more difficult to pin down and, indeed, considerable variability exists in the literature. An overview, however, of these factors leads to the following conclusions [12]. First, female gender is associated with decreased compliance perhaps because women are generally more likely to experience adverse effects of medication and more likely to seek counseling or make a decision about future compliance based on them. A prior history of good compliance is generally helpful in predicting future compliance because good habits are likely to carry over from one regimen to another. Single daily dosing is a key factor. Any drug that has to be taken more than once a day is associated with a considerable decline in compliance. Patients who have other diseases requiring intervention may likewise be less compliant because of the inability to remember and manage multiple treatment regimens. Surprisingly, a good health perspective generally decreases compliance perhaps because patients who feel healthy and energetic are less likely to be convinced of the need for therapy. Conversely, a bad health perspective generally improves compliance perhaps because patients who feel they are in poor health are more motivated to stick to the regimen.

The nature of the treatment regimen itself has an effect on compliance. As already stated, complex regimens are more likely to be poorly complied with. This is also true of costly regimens, as is demonstrated vividly in the post-trial follow-up in the 4S patients. Finally, a regimen that is perceived as having substantial side effects (even if that is not the case) is likely to illicit poor compliance [11].

The way physicians approach prescription of these regimens is also of importance in influencing compliance. An initial lack of clarity in recommendations is a prescription for enhancement of poor compliance, as is the failure to follow-up noncompliance when it is detected. Both of these behaviors may be reflections of the third physician factor that influences compliance, (*ie*, the perception on the part of the patient that the physician lacks commitment or belief in the efficacy of the regimen). Even if physicians have others within the practice setting who are primarily responsible for the prescription and monitoring of treatment and regimens, a perception on the part of the patient that the physician has minimal commitment to the regimen is very likely to lead to poor compliance [11].

The Canadian Coalition on High Blood Pressure Control has provided four simple steps for physicians and their staff to increase patient compliance. These are 1) the provision of written and verbal instructions that are clear and succinct; 2) the simplification of the regimen and the tailoring of the regimen to the individual patient; 3) the review and follow-up of compliance at each patient visit whether

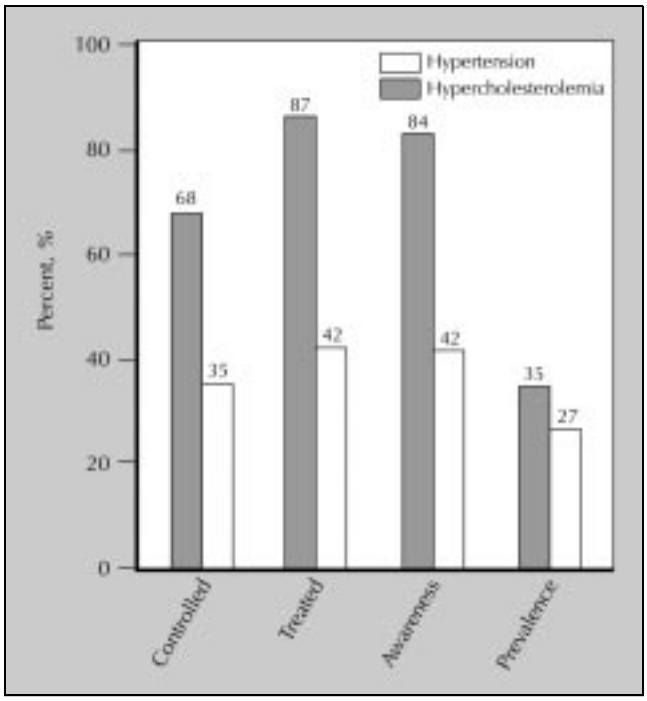

Figure 2. Awareness and treatment of high blood pressure versus hypercholesterolemia. (*Adapted from* Nieto *et al*. [15].)

the visit is primarily for that purpose or not; 4) the prescription of once-a-day regimens whenever possible [13].

Additional successful compliance strategies that may be used include 1) training patients in the skills and behaviors that will enhance compliance to whatever regimen has been prescribed; 2) training patients in self-monitoring so that they can keep a record of compliance and adjust their behavior accordingly; 3) the provision of regular telephone or mail contact to check patient self-monitoring and to indicate the continued interest of the health provider in the patient's successful compliance to the regimen; 4) "self-efficacy" enhancement, that is, training patients in steps to take on more and more responsibility for their own care; 5) cognitive aids for both the patient and medical staff including regular letters, chart reminders, and other devices to ensure that regular interim intermediate goals are achieved [14].

Public education also plays a vital role in achieving long-term compliance. If one compares hypertension and hypercholesterolemia with respect to the awareness of the condition among the public and among physicians, the prescription of treatment, and the successful control of the risk factor, hypertension is adequately treated and controlled in almost twice as high a percentage of patients as is hypercholesterolemia [15] (Fig. 2). The evidence that lowering cholesterol is beneficial is at least as good as that demonstrating the benefits of blood pressure control. Moreover, side effects from the drugs that treat hypertension are more bothersome than those currently associated with drugs available to treat hypercholesterolemia. It is likely, therefore, that the better rates of compliance and outcomes in hypertension are related to the greater opportunities for both public and physician education. If that is the case, then we can expect that as time goes by there will be little difference between the percentage of patients adequately treated and controlled with hypercholesterolemia and with hypertension.

Conclusions

Poor compliance with prescribed regimens remains a potent barrier to good outcomes in coronary heart disease and other chronic diseases. Such poor compliance is related to disease, patient, provider, and treatment factors and has yet to be fully understood. In general, the less complex the regimen, the better informed the patient and the physician, and the more serious the disease, the better the compliance.

That said, research information on compliance has been somewhat stagnant for several years. There have been very few new approaches that have broken new ground or significantly enhanced or altered correct approaches. It is probably necessary that future research involve nonmedical disciplines including motivational psychology and even advertising. A good deal of such research should be specifically directed toward improving compliance in asymptomatic patients who are nevertheless at substantial risk of future catastrophic events. Until we are more successful at reproducibly improving compliance in high-risk, but asymptomatic, patients, the potential benefits of regimens whose efficacy is already very clear will remain unfulfilled.

References

1. LaRosa JC, He J, Vupputuri S: **Effect of statin drug treatment on risk of coronary heart disease: a meta-analysis of randomized, controlled trials.** *JAMA*, 1999, in press.
2. Kannel W: **Clinical misconceptions dispelled by epidemiological research.** *Circulation* 1995, **92:**3350–3360.
3. *Random House Dictionary,* edn. 2. New York: 1982.
4. Elliott WJ: **Compliance strategies.** *Curr Opin Nephrol Hypertens* 1994, **3:**271–278.
5. Delacretaz E, Michalopoulos PG, Ruiz J, *et al.*: **Management of hyperlipidaemia after coronary revascularisation: follow up study.** *BMJ* 1998, **316:**1499.
6. Shepherd J, Pratt M: **Prevention of coronary heart disease in clinical practice: a commentary on current treatment patterns in six European countries in relation published recommendations.** *Cardiology* 1996, **87:**1–5.
7. Avorn J, Monette J, Lacour A, *et al.*: **Persistence of use of lipid-lowering medications: a cross-national study.** *JAMA* 1998, **279:**1458–1462.
8. Strandberg TE, Lehto S, Pyorala A, *et al.*: **Cholesterol lowering after participation in the Scandinavian Simvastatin Survival Study (4S) in Finland.** *Eur Heart J* 1997, **18:**1725–1727.
9. Andrade SE, Walker AM, Gottlieb LK, *et al.*: **Discontinuation of antihyperlipidemic drugs—do rates reported in clinical trials reflect rates in primary care settings?** *N Engl J Med* 1995, **332:**1125–1131.
10. McDermott MM, Schmitt B, Wallner E: **Impact of medication nonadherence on coronary heart disease outcomes: a critical review.** *Arch Intern Med* 1997, **157:**1921–1929.
11. Luepker RV: **Patient adherence: a "risk factor" for cardiovascular disease.** *Heart Dis Stroke* 1993, **2:**418–421.

12. Sung JC, Nichol MB, Venturini F, *et al.*: **Factors affecting patient compliance with antihyperlipidemic medications in an HMO population.** *Am J Manag Care* 1998, **4:**1421–1430.
13. Chockalingam A, Bacher M, Campbell N, *et al.*: **Adherence to management of high blood pressure: recommendations of the Canadian Coalition for High Blood Pressure Prevention and Control.** *Can J Pub Health* 1998, **89:**I5–I7.
14. Burke LE, Dunbar-Jacob JM, Hill MN: **Compliance with cardiovascular disease prevention strategies: a review of the research.** *Ann Behav Med* 1997, **19:**239–263.
15. Nieto FJ, Alonso J, Chambless LE, *et al.*: **Population awareness and control of hypertension and hypercholesterolemia: The Atherosclerosis Risk in Communities study.** *Arch Intern Med* 1995, **155:**677–684.